An Integrative Approach to Breast Cancer

Tara Scott, MD, FACOG, FAAFM, ABOIM, CNMP

HORMONE GURU

**no financial relationships to disclose*

What are we going to cover today?

- Review hormone physiology as it pertains to cancer
- Discuss different types of testing to assess estrogen load at the tissue levels
- Discuss estrogen metabolism and discuss how it relates to cancer
- Review the Evidence about HRT and cancer

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WHO Am I?

- Tara Scott, MD
- Board certifications in: OB/GYN, Integrative Medicine, and Anti-Aging, Functional and Regenerative Medicine
- Lecture around the world teaching doctors a functional approach to women's health
- Medical Director of Forum Health in Akron, OH

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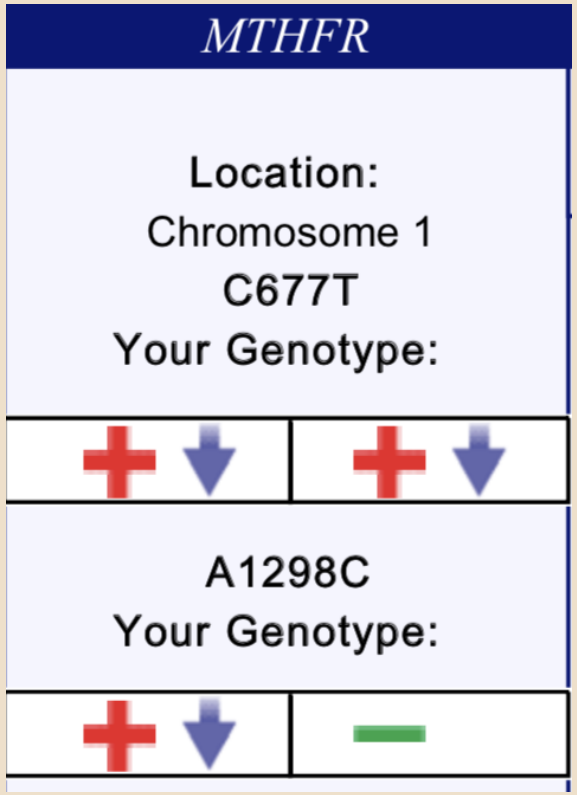
I've got *Bad Genes!*

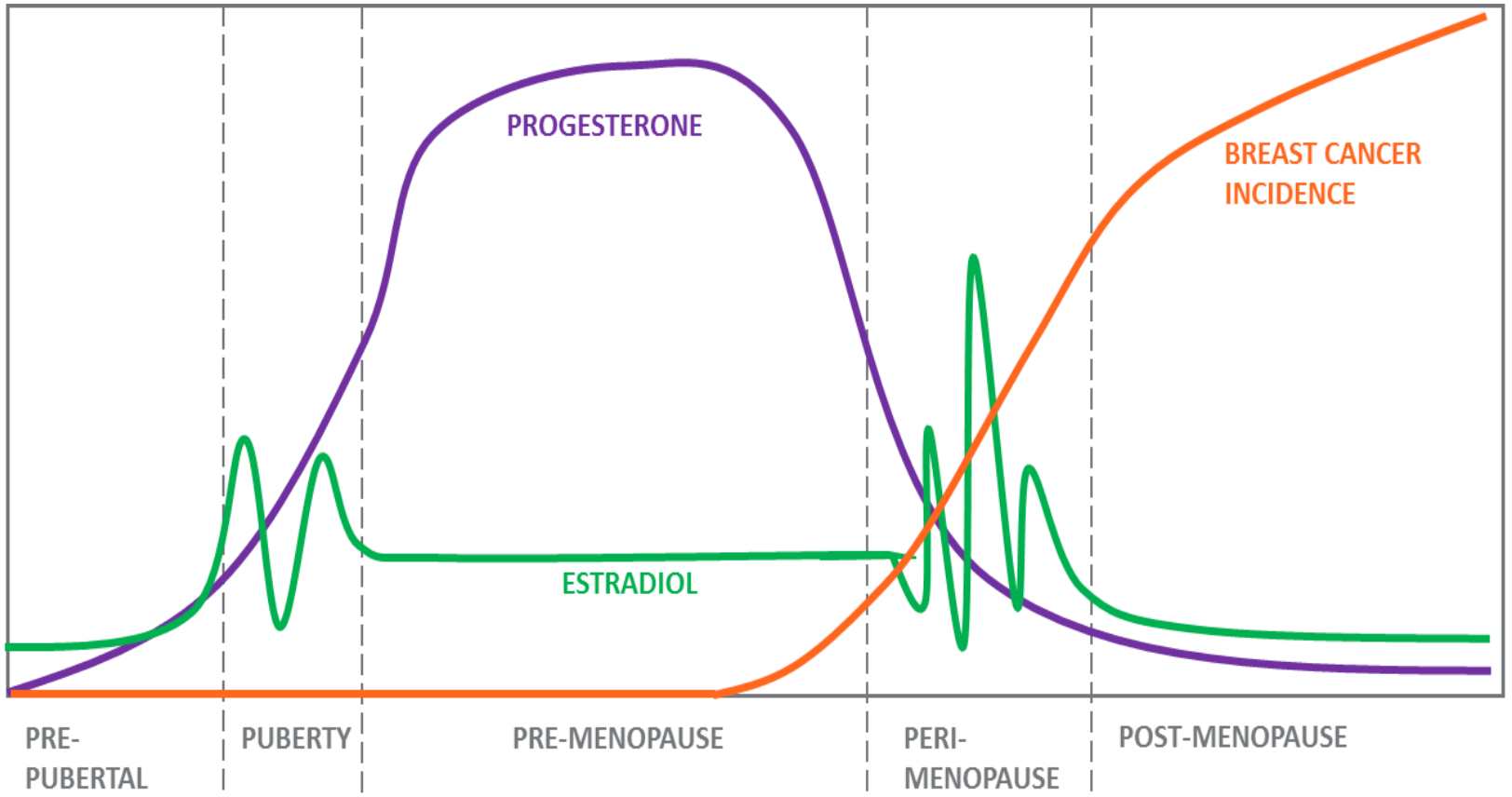
Detoxification Oestrogen	CYP17A1	-34T>C	A/G	
	CYP1A1	Msp1 T>C	T/C	
		2454A>G (Ile462Val)	T/T	
	CYP1B1	4326C>G (Val432Leu)	G/G	
	GSTM1	519G>C	G/G	
	GSTT1	15G>C	C/C	
	NQO1	609C>T	C/T	
	SULT1A1	638G>A	G/G	
Methylation Oestrogen	COMT	472G>A (Val158Met)	A/G	
	MTHFR	677C>T	AA	
Oxidative Stress Oestrogen	SOD2	-28C>T (Ala16Val)	C/C	
Thrombosis	F5	G1691A	CC	



In Memory of Laura 4/1/85-1/23/19

Estrogen Metabolism & Breast Cancer

Samavat & Kurzer, 2015



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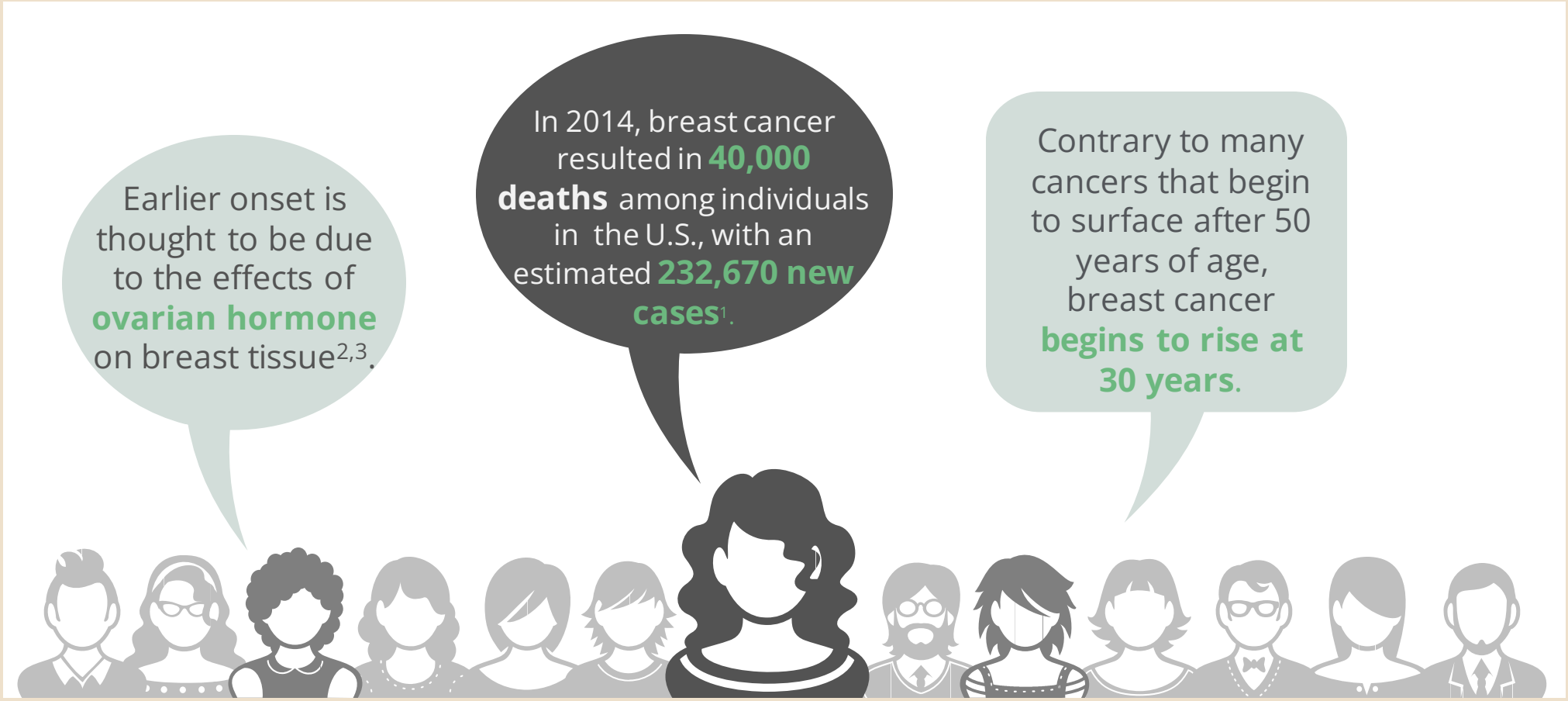
Estrogen Metabolism & Breast Cancer



1. Siegel et al., 2014
2. Howlader et al., 2013
3. Hulka & Moorman, 2001

Breast Cancer Risk Factors

- Age
- BRCA1 & BRCA2 gene mutations
- Family History
- Reproductive History
- Radiation History
- Elevated Endogenous Estrogen Levels
- Hormone Therapy
- Obesity
- Alcohol

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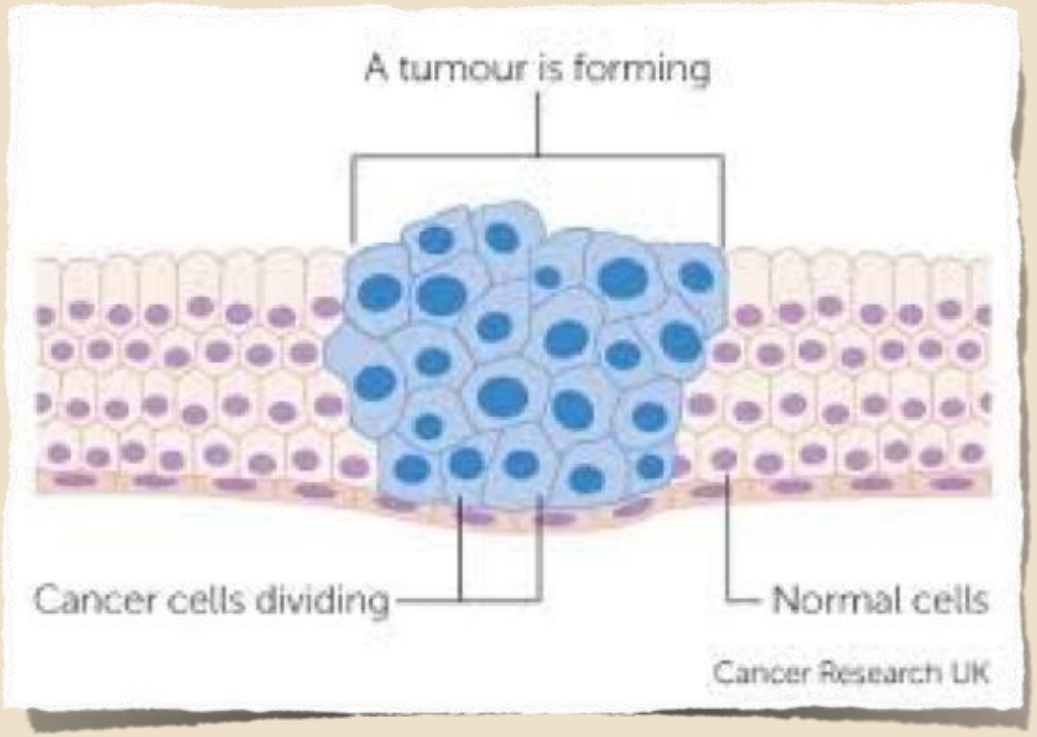
Samavat & Kurzer, 2015

What is Cancer?



- Cancer is the failure of the immune system to get rid of abnormal cells before they take root and become full blown cancer
- A healthy cell metabolizes oxygen and glucose from food, producing ATP (aerobic)

- Cancer cells (anaerobic) siphon off glucose from healthy cells to have energy to grow and spread

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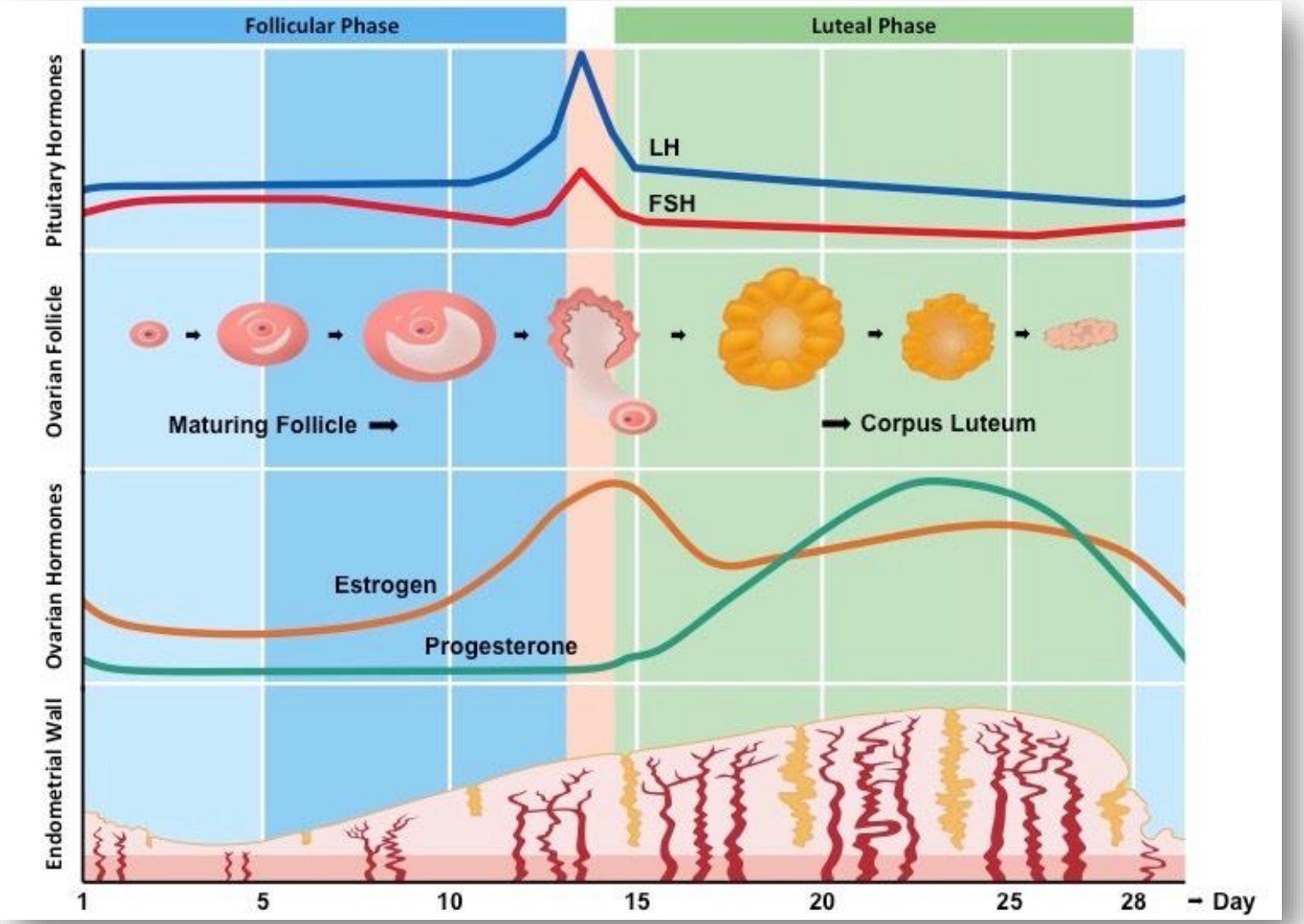

Menstrual Cycle

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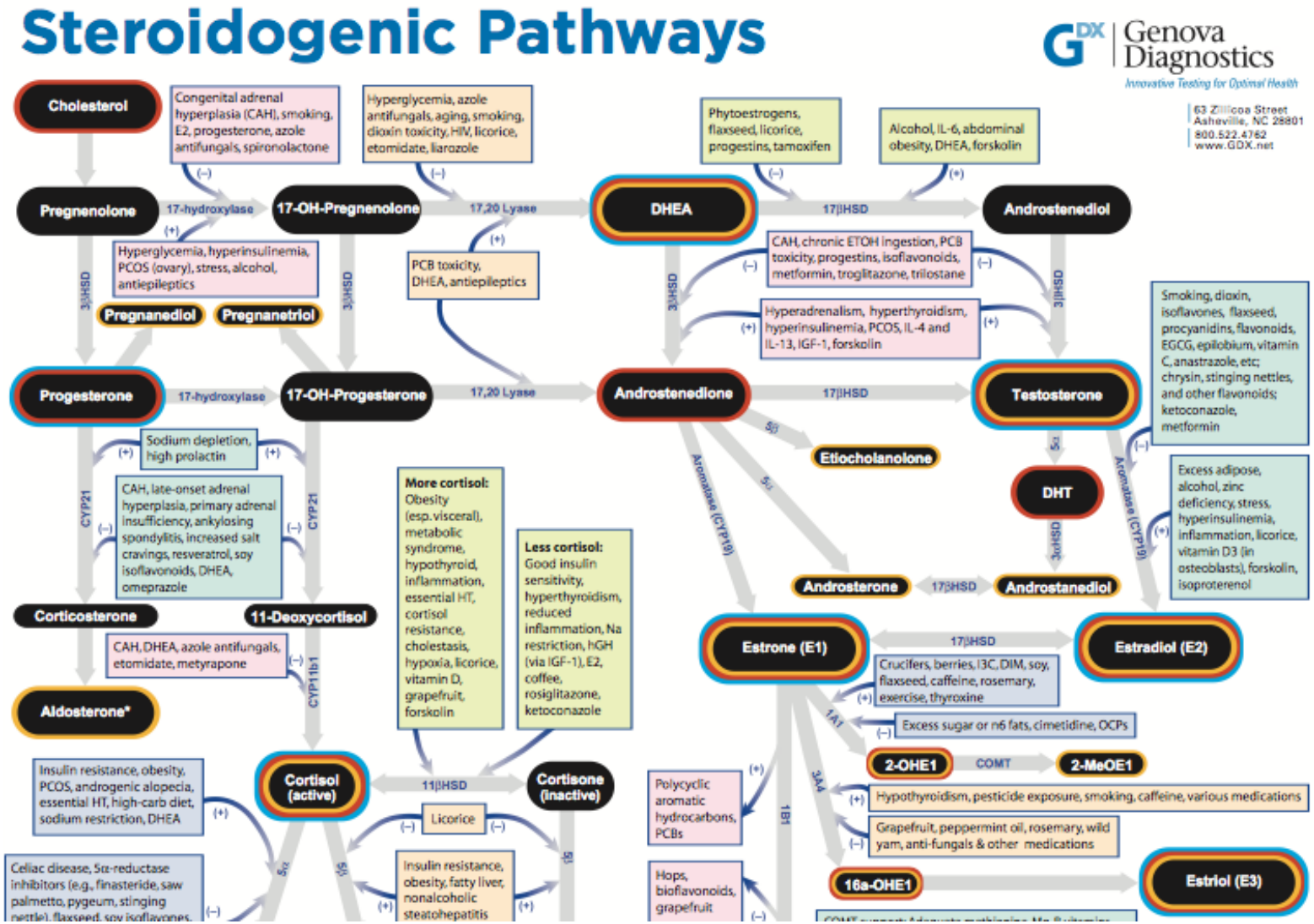

Steroidogenic Pathways

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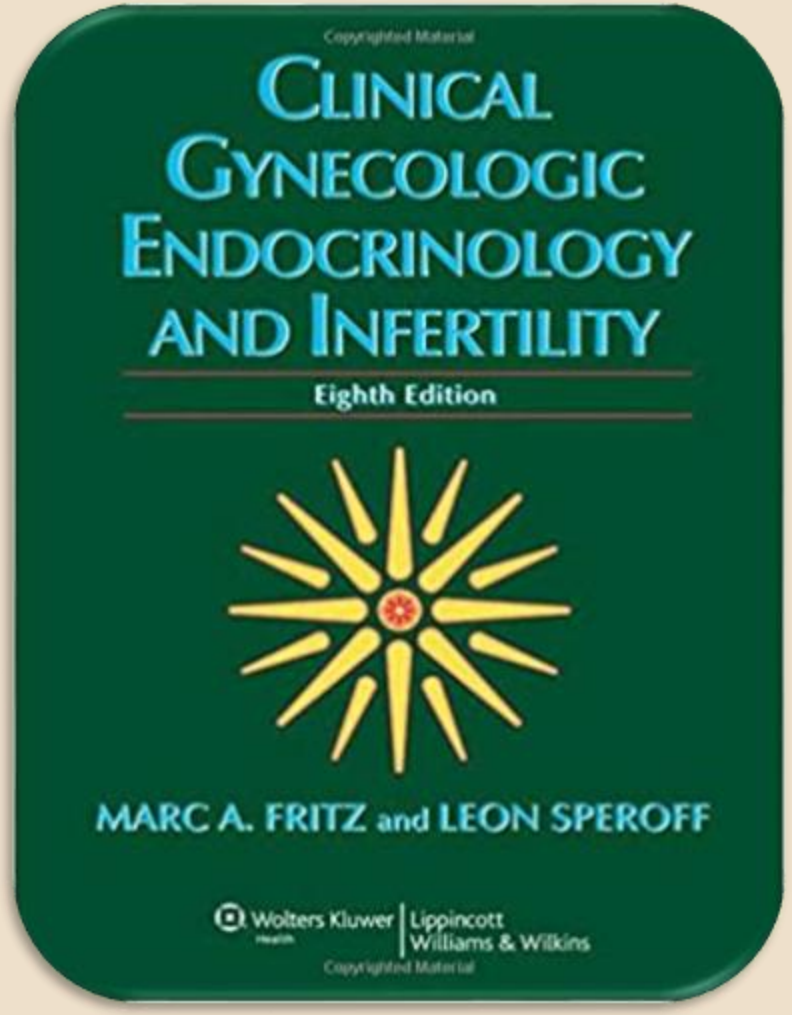
What do we Know?



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Pearls from Dr. Speroff

Estrogen causes proliferation

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Progesterone Inhibits proliferation, decline in DNA synthesis, interferes with the estrogen receptor

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Estrogen stimulates many oncogenes that mediate estrogen induced growth. Progesterone antagonizes this action- suppresses transcription of oncogene mRNA

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Breast and endometrial cells are similar

Page 624

Estrogen Functions

- Promotes growth
- Body development
- Slows bone loss
- Three main types
  - Estradiol- good for heart and bones
  - Estriol - good for skin
  - Estrone- goes to breast- sort of the bad one

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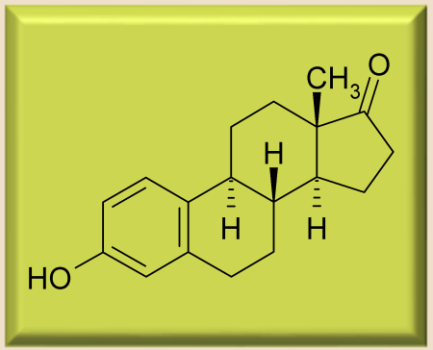
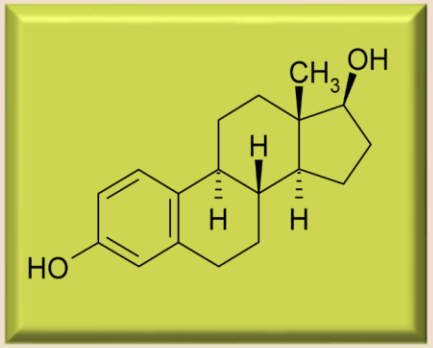
Types of Estrogen



Estrone (E1)

Primarily synthesized from **androstenedione** by aromatase conversion in the ovaries.

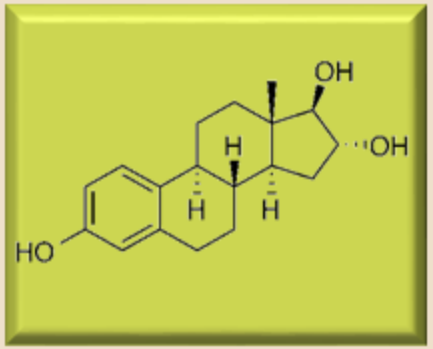
Reversibly converted into estradiol by enzyme, 17β-hydroxysteroid dehydrogenase Type II.



Estradiol (E2)

Primarily synthesized by **developing follicle** in the ovaries.

Reversibly converted into estrone by enzyme, 17β-hydroxysteroid dehydrogenase Type I.



Estriol (E3)

Synthesized from **estrone**, which can be converted from the hydroxylation of estradiol or 16-Hydroxyestrone.

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I think of Estrogen like three sisters

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Not All Estrogens act the SAME

There is an alpha and beta estrogen receptors in every cell in our body

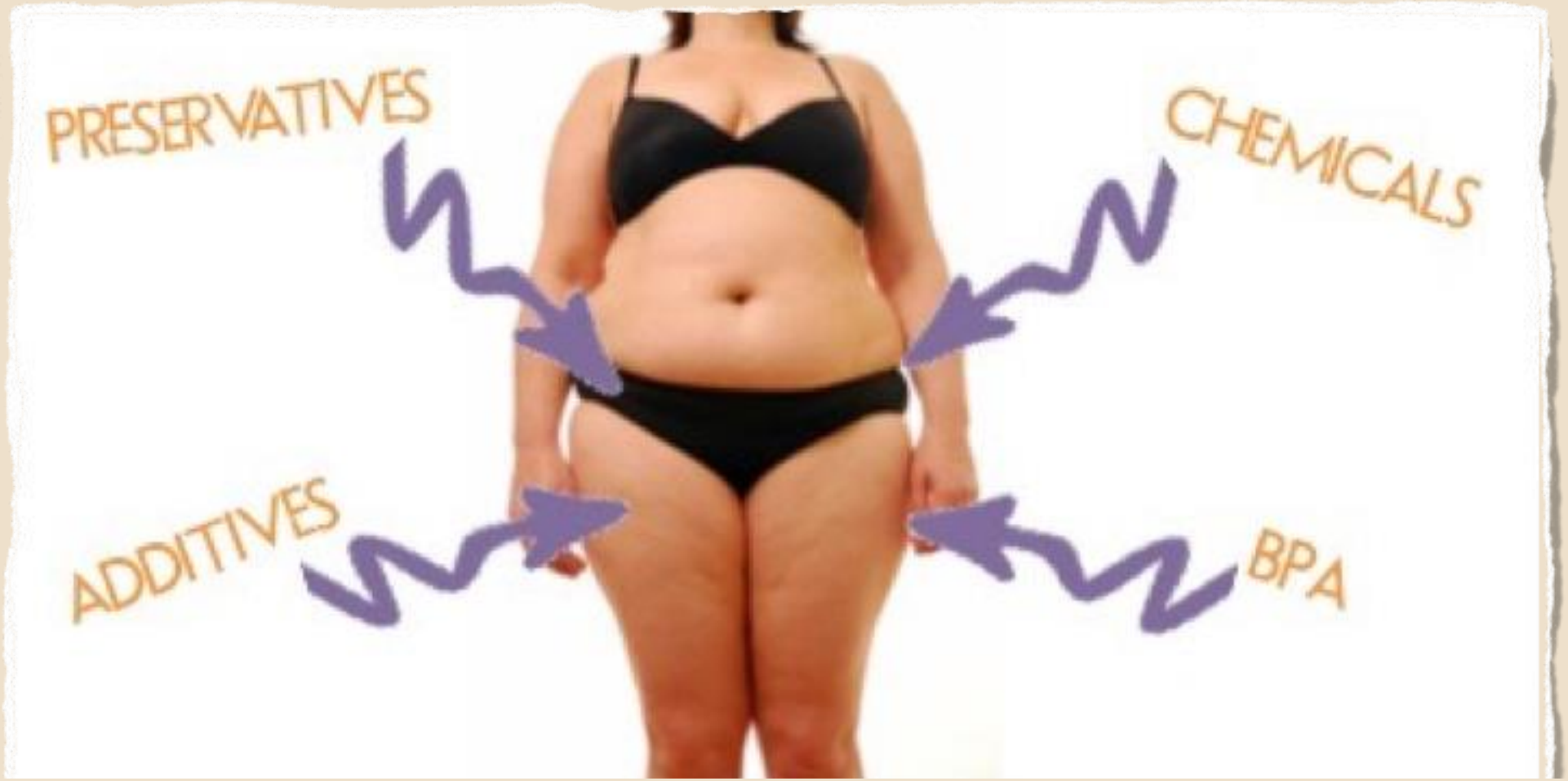
For example, in terms of breast cancer, activation of estrogen receptor-alpha is associated with breast cell proliferation, while activation of estrogen receptor-beta prevents breast cancer development (Paruthiyil et al., 2004).

Estrone favorably binds the alpha receptor with a 5:1 ratio, while Estriol favors the beta receptor

Boothby, Lisa A., et Al. "Bio identical hormone therapy: a review" in *Menopause,* 2004, vol 11, No. 3, pp.356-367

	Estrogen Receptor-Alpha	Estrogen Receptor-Beta
17- Beta-estradiol	100	100
17- alpha-estradiol	58	11
Estriol	14	21
Estrone	60	37
4-OH-Estradiol	13	7
2-OH-Estrone	2	0.2
Tamoxifen	4	3
Raloxifene	69	16

Other sources of Estrogen



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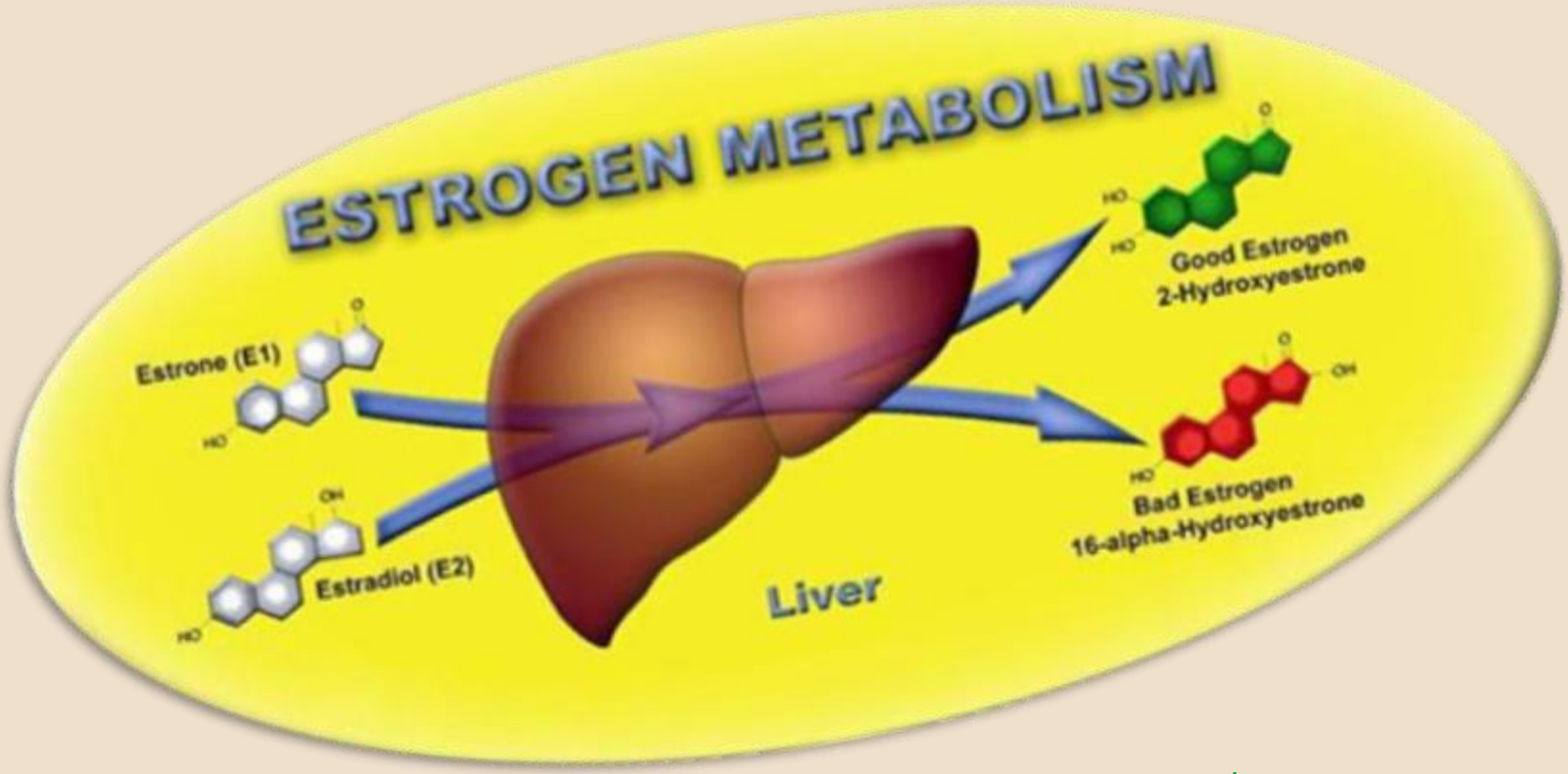
Reasons you might have high Estrogens



- You make a lot
- Environment, diet
- Genetics - You can't get rid of it
- You have had a hysterectomy and are only taking estrogen, not progesterone

2-Hydroxyestrone

16-alpha-Hydroxyestrone

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Functions of Progesterone

- Antidepressant
- Helps use fat for energy
- Helps thyroid functions
- Stimulates bone building
- Maintains libido/ sexual desire
- Promotes sleep
- Helps with memory

Protects against

- ✓ Fibrocystic Breast Disease
- ✓ Breast/ Endometrial Cancer
- ✓ Osteoporosis
- ✓ Heart Disease
- ✓ Mental Decline

Functions of Testosterone

Protects against

- ✓ Libido
- ✓ Muscle strength
- ✓ Stamina
- ✓ Increasing bone mineral density and preventing further decline into osteoporosis
- ✓ Maintaining lean body mass, strength and stamina
- ✓ Improved mood, memory and structural integrity of the brain itself

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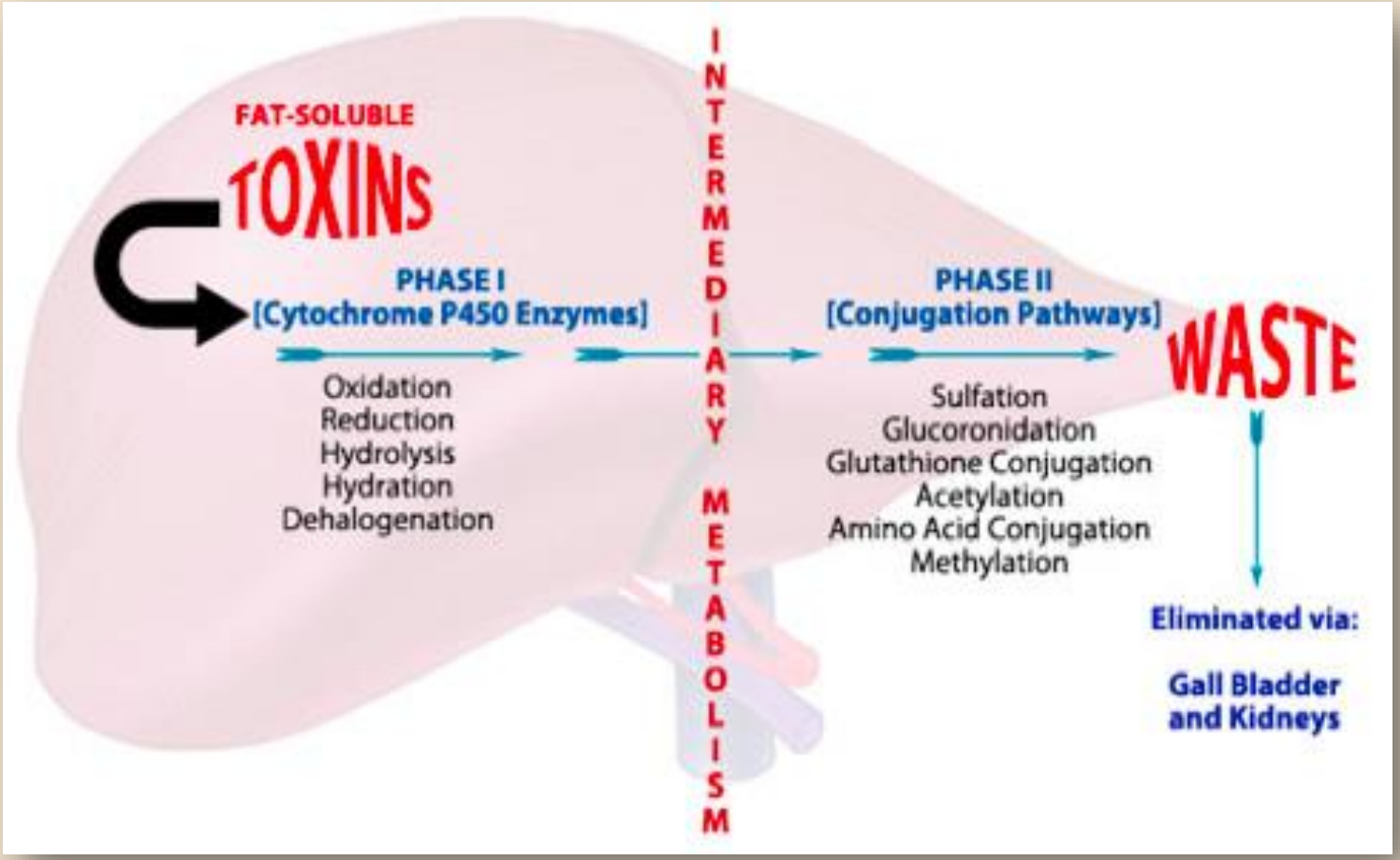
Phases of Detoxification



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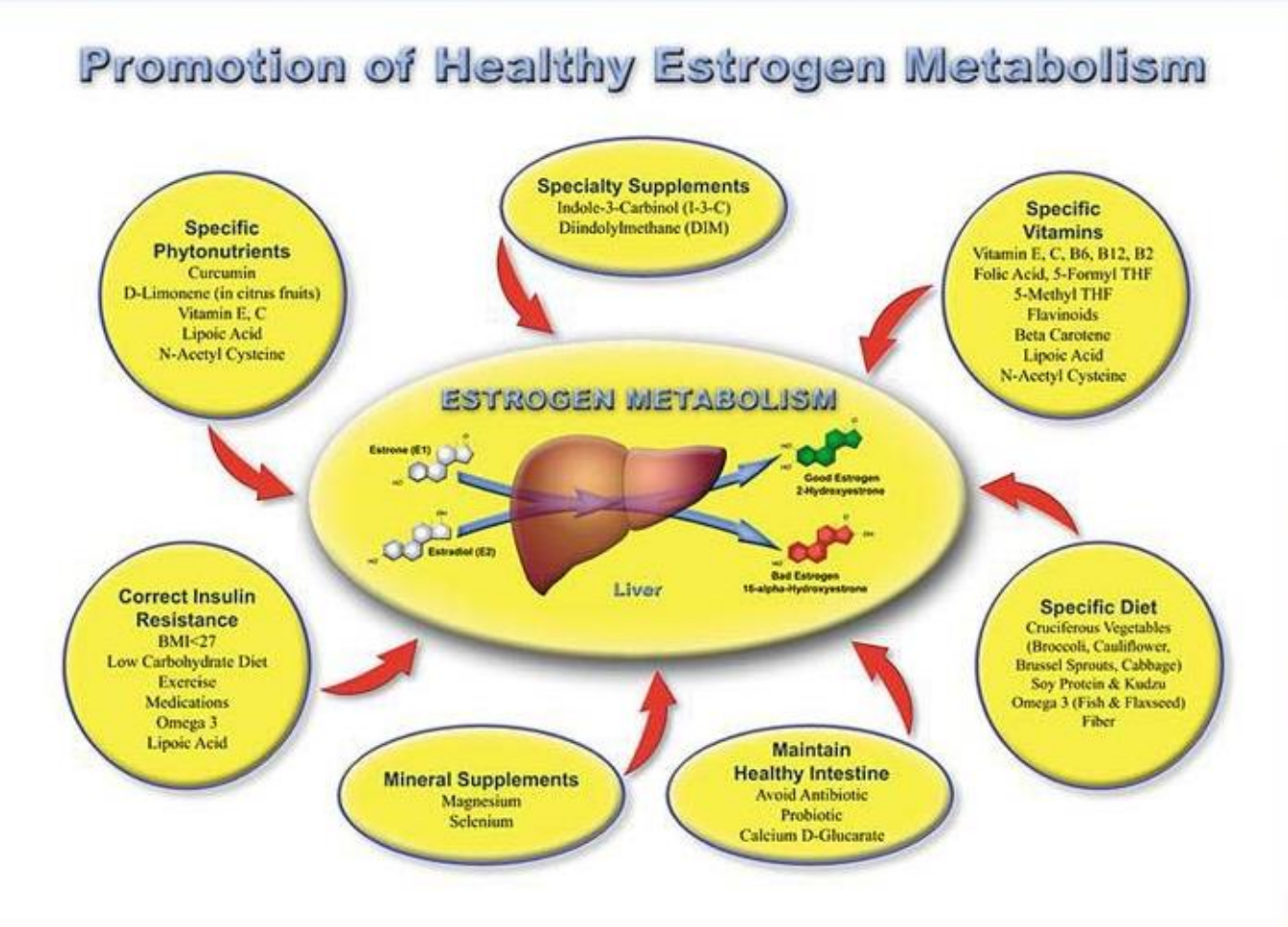
Healthy Estrogen Metabolism

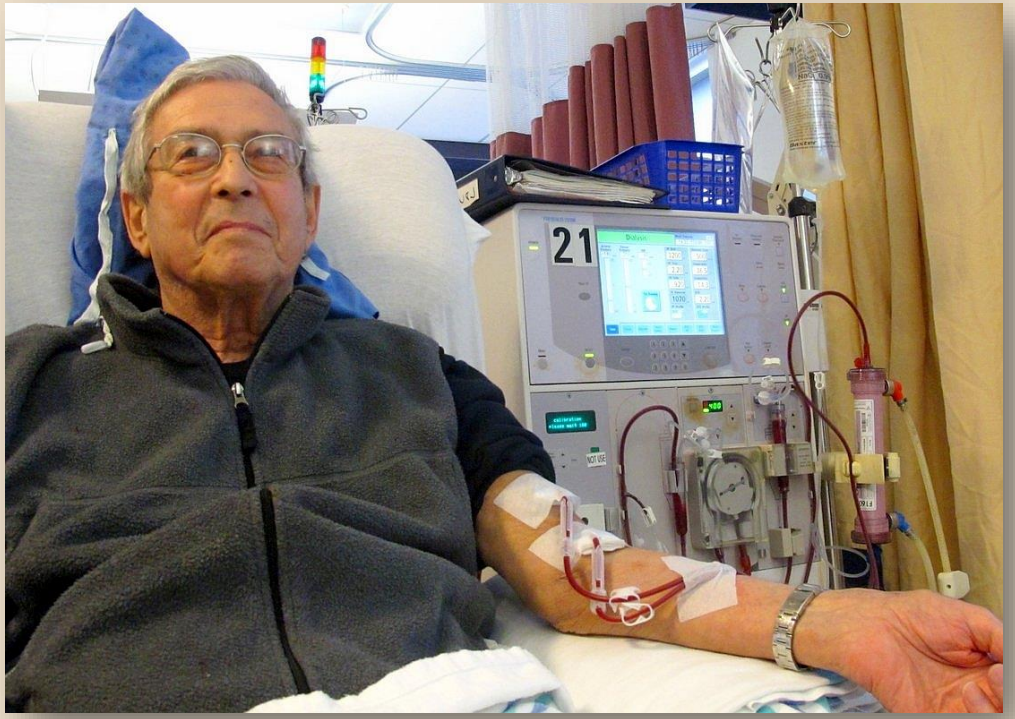


- Specific Phytonutrients
- Specific Supplements
- Specific Vitamins
- Specific Diet
- Healthy Intestine
- Minerals
- Correct Insulin Resistance

Suppose I tell all my patients to drink 2 liters of water

- Marathon Runner in 80 degree weather

- Dialysis Patient



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Why is it so important to check estrogen metabolism?

Is it really possible to have a randomized placebo controlled trial with hormone therapy?

?

You need to consider:

- Weight, age, oophorectomy status
- Pharmacokinetics: what the body does to the drug
- Pharmacodynamics: what the drug does to the body

Pearls from Dr. Speroff

Estrogen causes proliferation

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Progesterone Inhibits proliferation, decline in DNA synthesis, interferes with the estrogen receptor

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Estrogen stimulates many oncogenes that mediate estrogen induced growth. Progesterone antagonizes this action- suppresses transcription of oncogene mRNA

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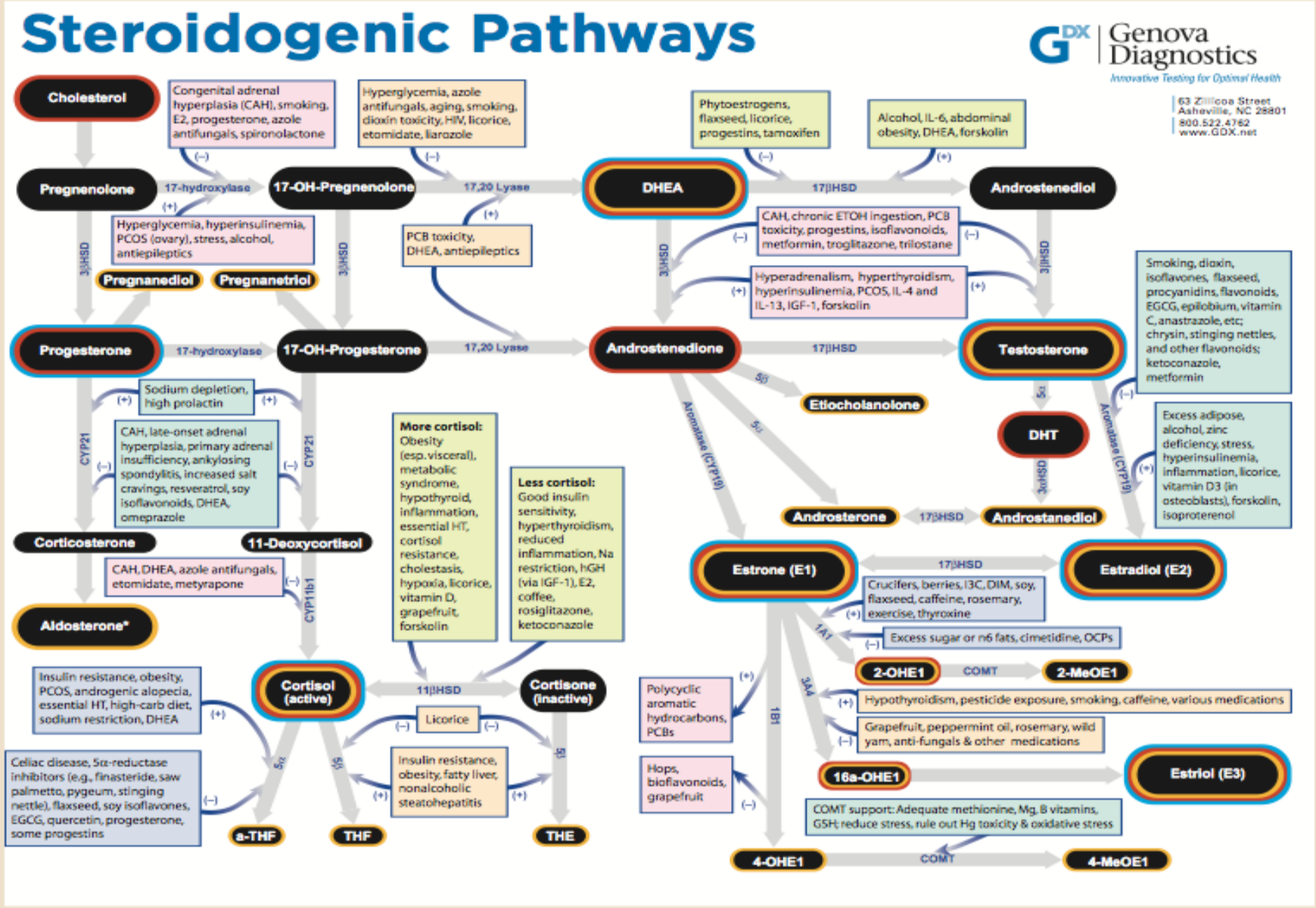
Steroidogenic Pathways



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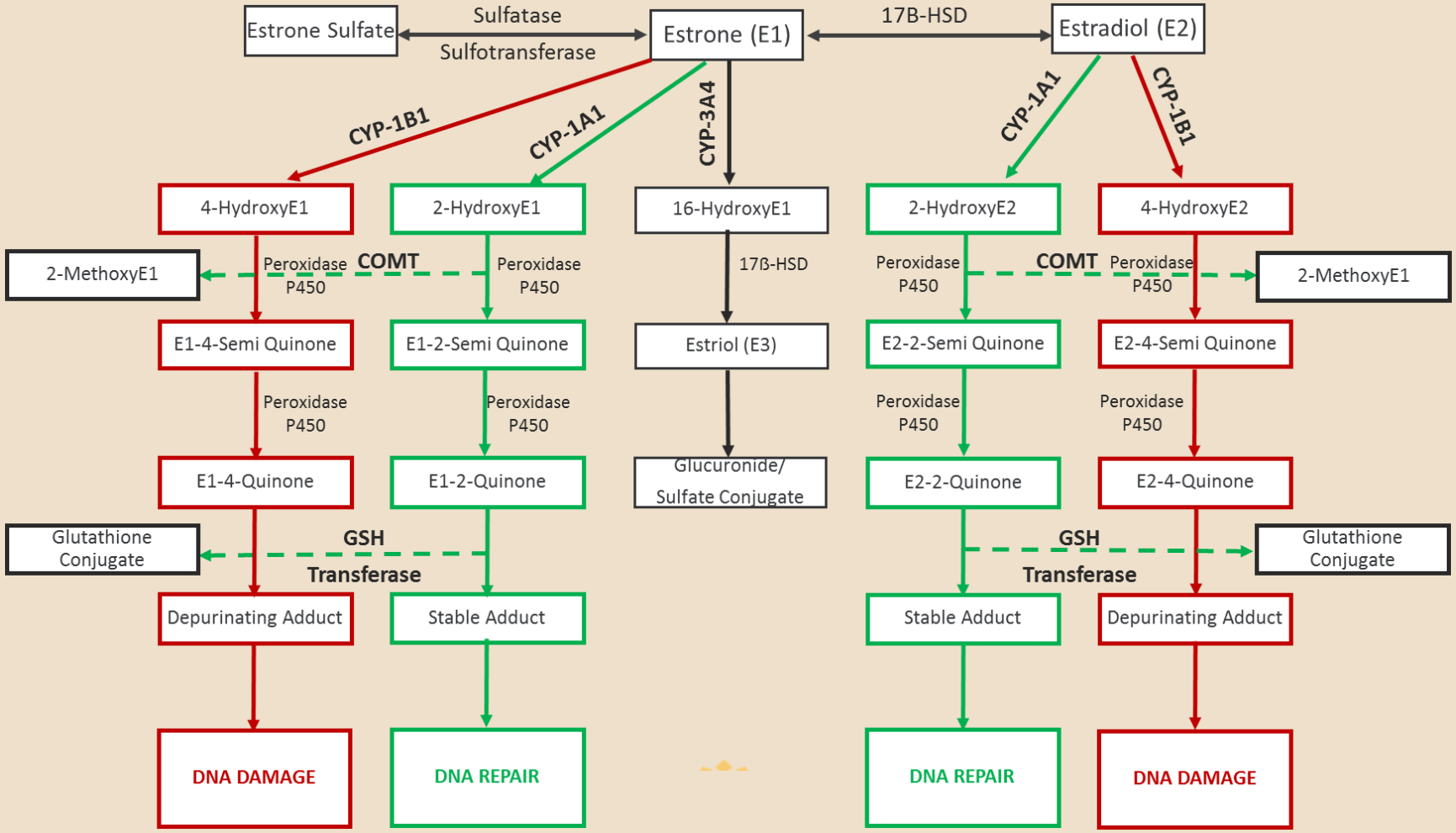
Estrogen Metabolism



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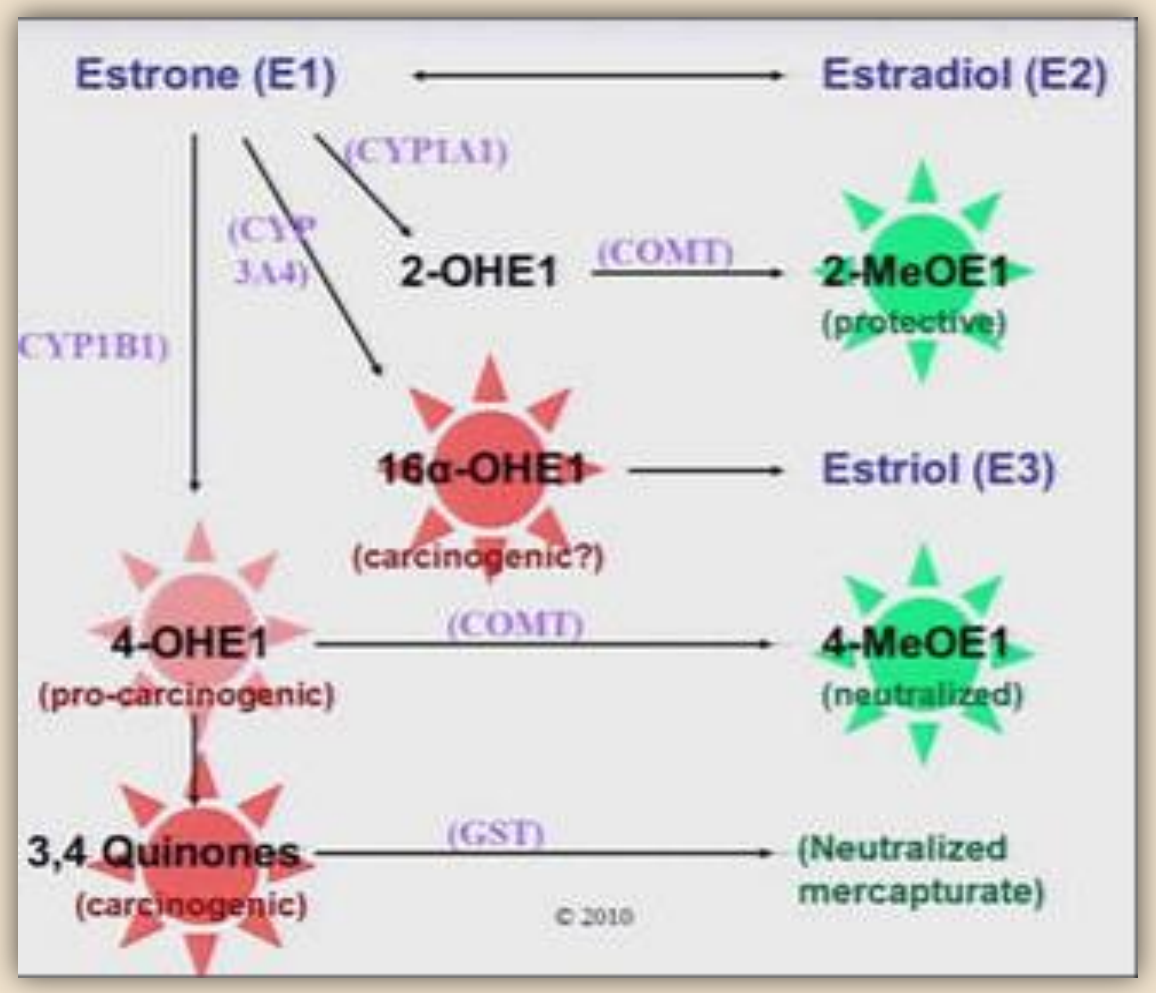
Estrogen Metabolism

- More simplified . . .



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The "Good" Estrogens

Considerable weak with overall low hormonal potency and low binding affinity to estrogen receptors[1].

2-hydroxyestrogen have anti-proliferative effects in breast tissue[1,2].

Estrogen Metabolites

Samavat & Kurzer, 2015

Gupta et al., 1998

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The "Good" Estrogens

METHOXYESTROGENS:

- Methoxyestrogens are deactivated forms of estrogen formed from methylation of catechol estrogens.
- This methylation conjugation prevents the biotransformation of hydroxyestrogens into quinone-DNA adducts (DNA damage) and the byproduct formation of reactive oxygen species.
- Methoxyestrogens also inhibits cell proliferation by inhibiting mitosis[1,2.3].

Estrogen Metabolites

1. Dawling et al., 2003

2. Lakhani et al., 2003

3. Lottering et al., 1992

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The "Bad" Estrogens

4-HYDROXYESTROGEN QUINONE METABOLITES

- Lead to the formation of depurinating adducts[1].
- Women with or at high risk for breast cancer had high levels of adducts in their urine[2].
- In cellular preparations of adenocarcinoma, 4-hydroxyestradiol was 4x higher than 2-hydroxyestradiol[3].

Estrogen Metabolites

1. Cavalieri et al., 1997
2. Cavalieri & Rogan, 2010
3. Liehr & Ricci, 1996

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The "Bad" Estrogens

16α-HYDROXYESTRONE

- 16α-Hydroxyestrone is the intermediate between estrone and estriol.
- Higher urinary concentrations of 16α-Hydroxyestrone were associated with mammary cell proliferation in animals[1].
- 16α-Hydroxyestrone has been found to be higher cancer breast tissue relative to normal breast tissue[2].
- 16α-Hydroxyestrone is inversely proportional to 2-hydroxyestrone.
- Recent evidence has drawn into question the significance in the 16α-Hydroxyestrone breast cancer relation[3,4].

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Estrogen Metabolites

1.Telang et al., 1992

2.Castagnetta et al., 2002

3.Obi et al., 2011

4.Huang et al., 2012

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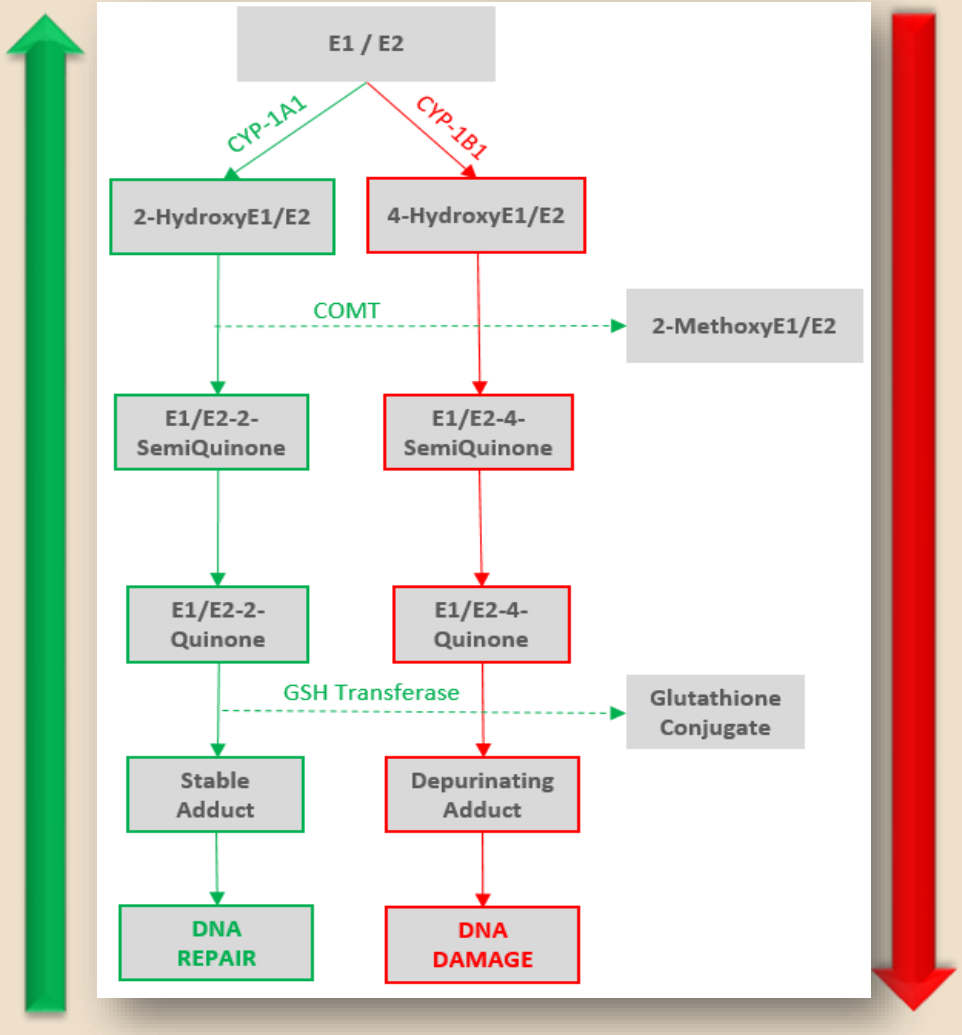
Preventing Negative Estrogen Burden

Increase **2-HydroxyE** Pathway Activity



Reduce **4-HydroxyE** Pathway Activity

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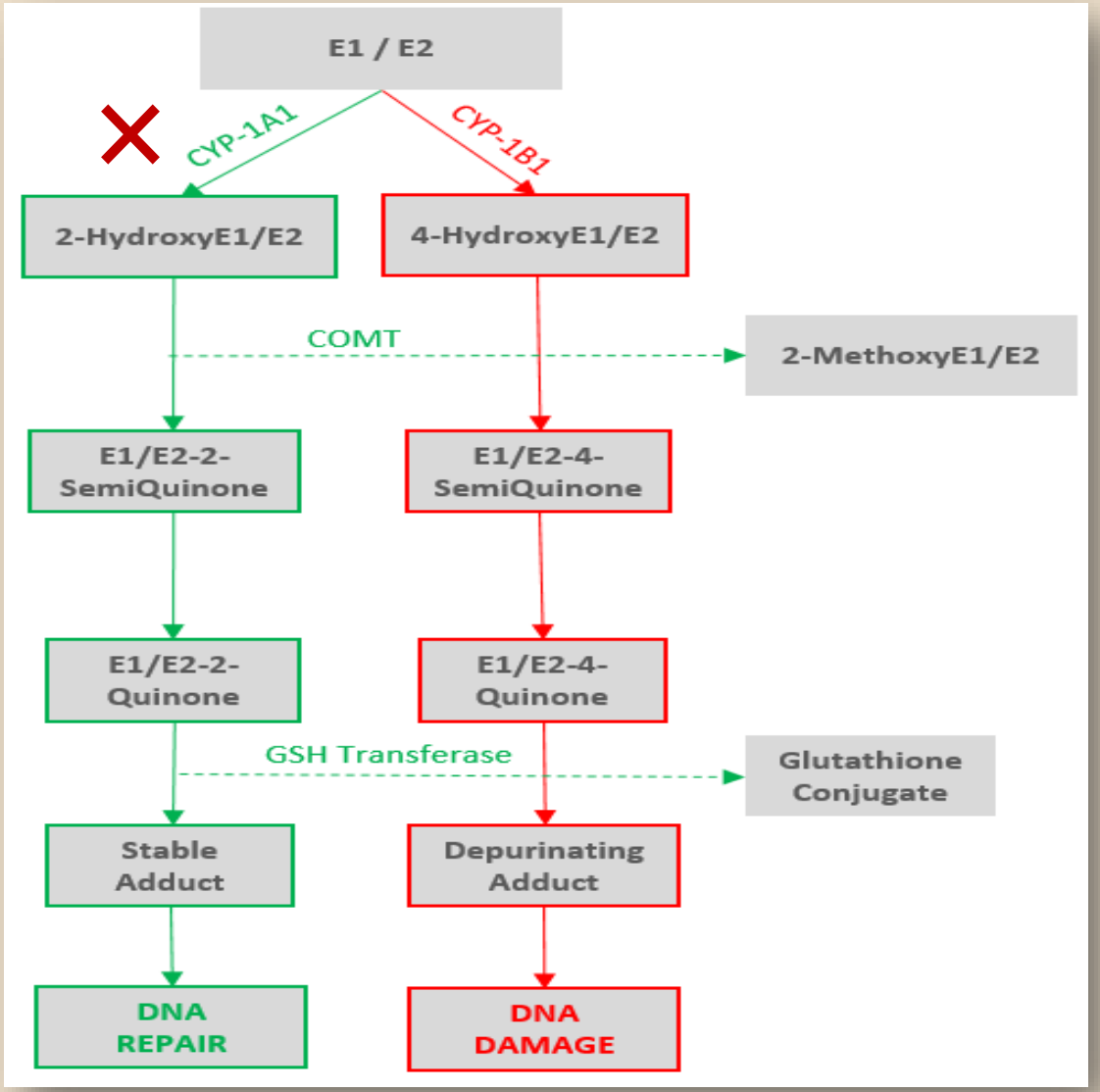
Preventing Negative Estrogen Burden

INSECTICIDES (e.g., endosulfan) has been found to inhibit the expression of CYP-1A1, resulting in reduced activity of the 2-hydroxyE pathway[1].

1. Coumoul et al., 2001



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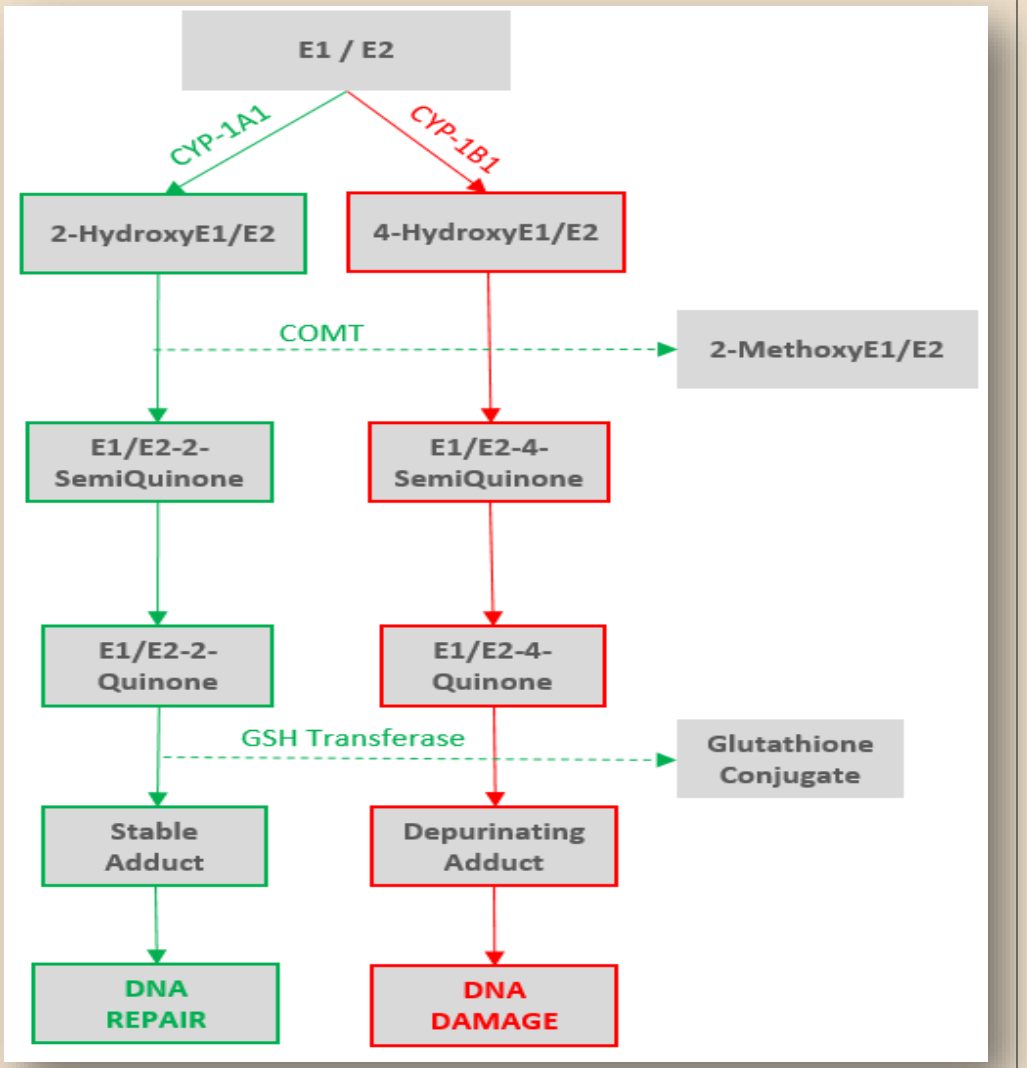
Preventing Negative Estrogen Burden

RESVERATROL prevents the formation of depurinating estrogen DNA adducts in human breast cells treated with E[1].

Resveratrol inhibits peroxidase activity, reducing the formation of catechol estrogen quinones[1].

Resveratrol also increases NDPH quinone reductase activity[2].



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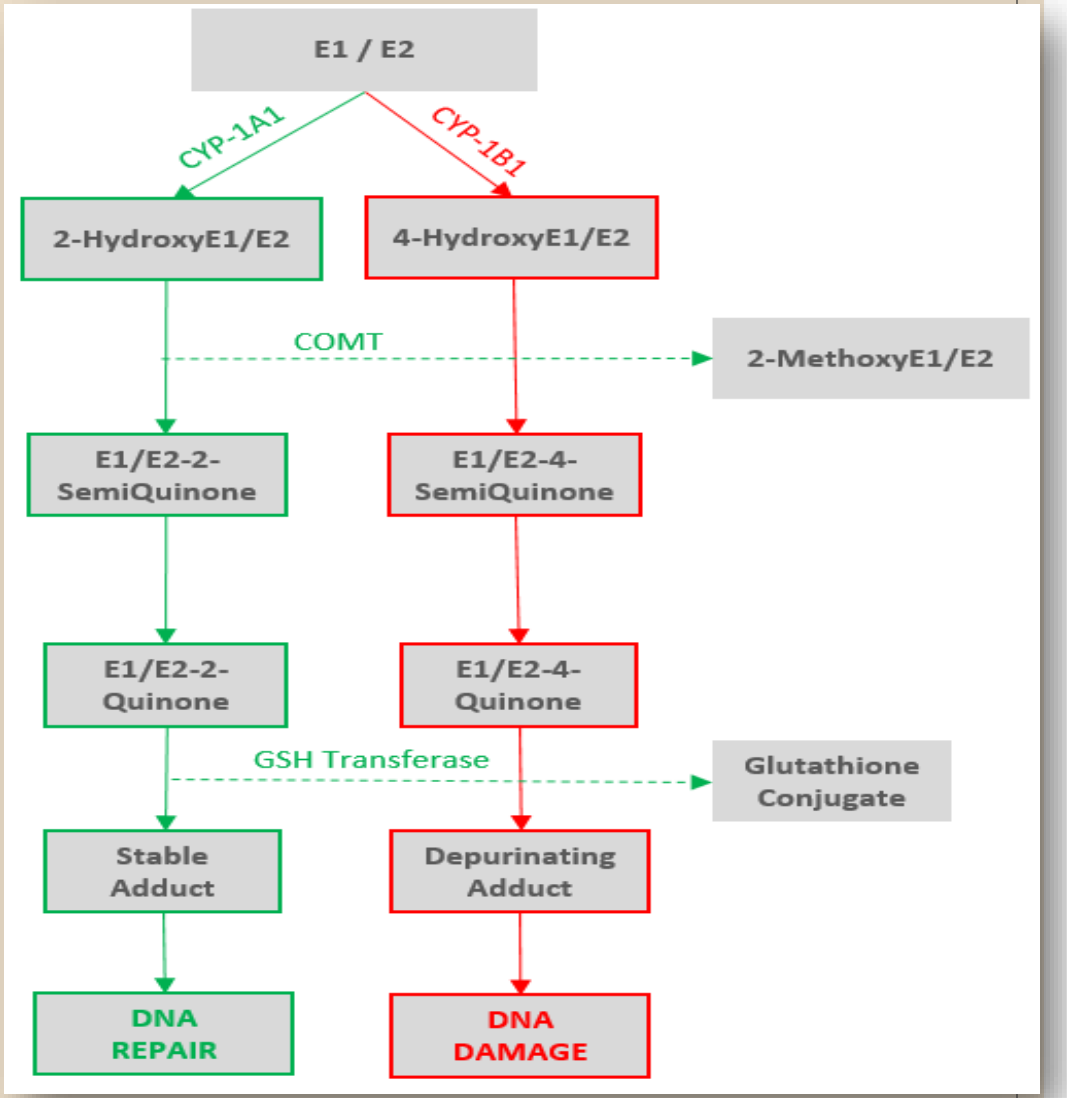
1. Cavalieri & Rogan, 2010
2. Zahid et al, 2008

Preventing Negative Estrogen Burden

N-ACETYLCYSTEINE prevents electrophilic damage to DNA by inhibiting the formation electrophilic quinones.

It has been found that the consumption of N-acetylcysteine for a 1-month period resulted in 55% reduction in urinary levels of estrogen DNA adducts[1].



1. Cavalieri & Rogan, 2010
2. Zahid et al., 2008

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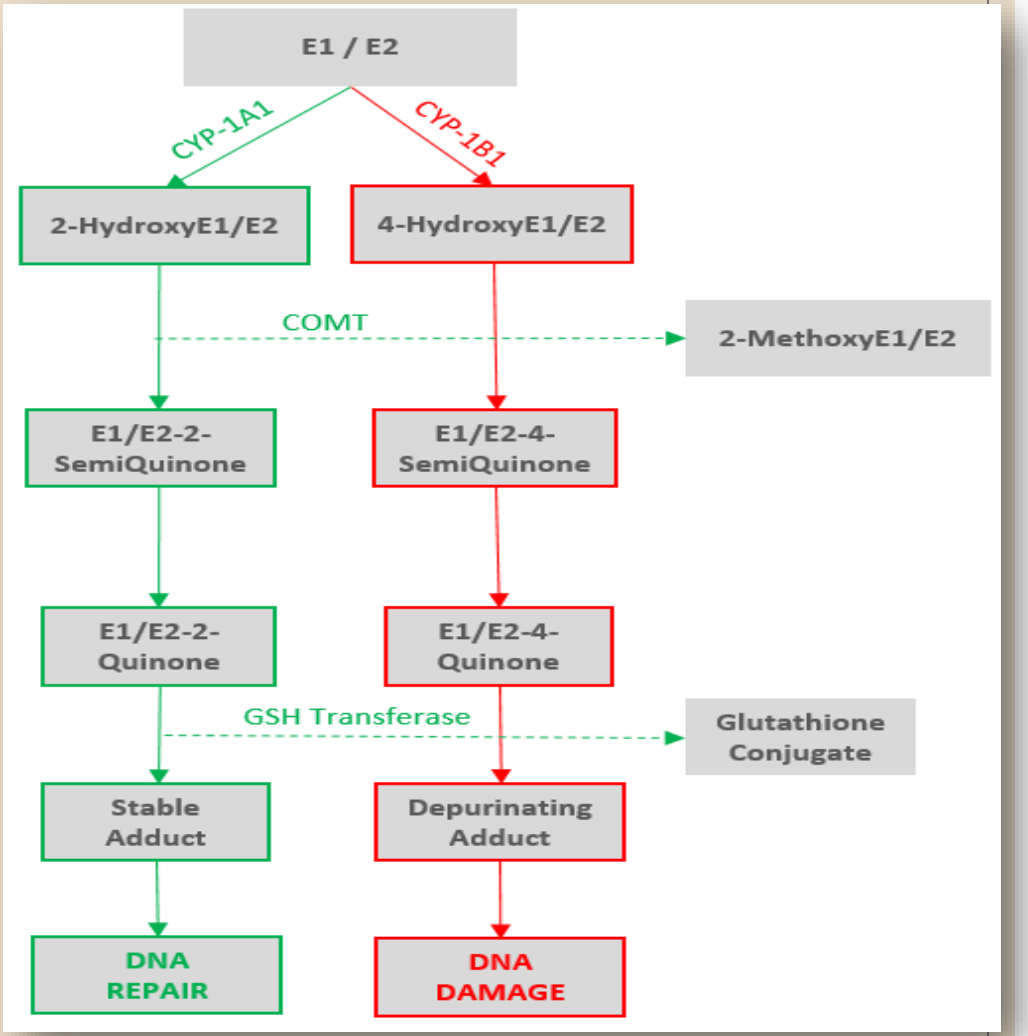
Preventing Negative Estrogen Burden

IODINE supplementation is effective at diminishing ductal hyperplasia in rats[1].

Patients with benign breast disease that received iodine treatment experienced significant bilateral breast reduction[2].

Japanese communities that consume high amounts of seaweed (high [I]) have reported lower incidences of benign and malignant tissue[3].

Iodine is thought to exhibit its beneficial effects by modulating estrogen metabolism[4,5].



1. Eskin et al., 1995
2. Ghent et al., 1993
3. Cann et al., 2000
4. Snyth, 2003
5. Stoddard II et al., 2008

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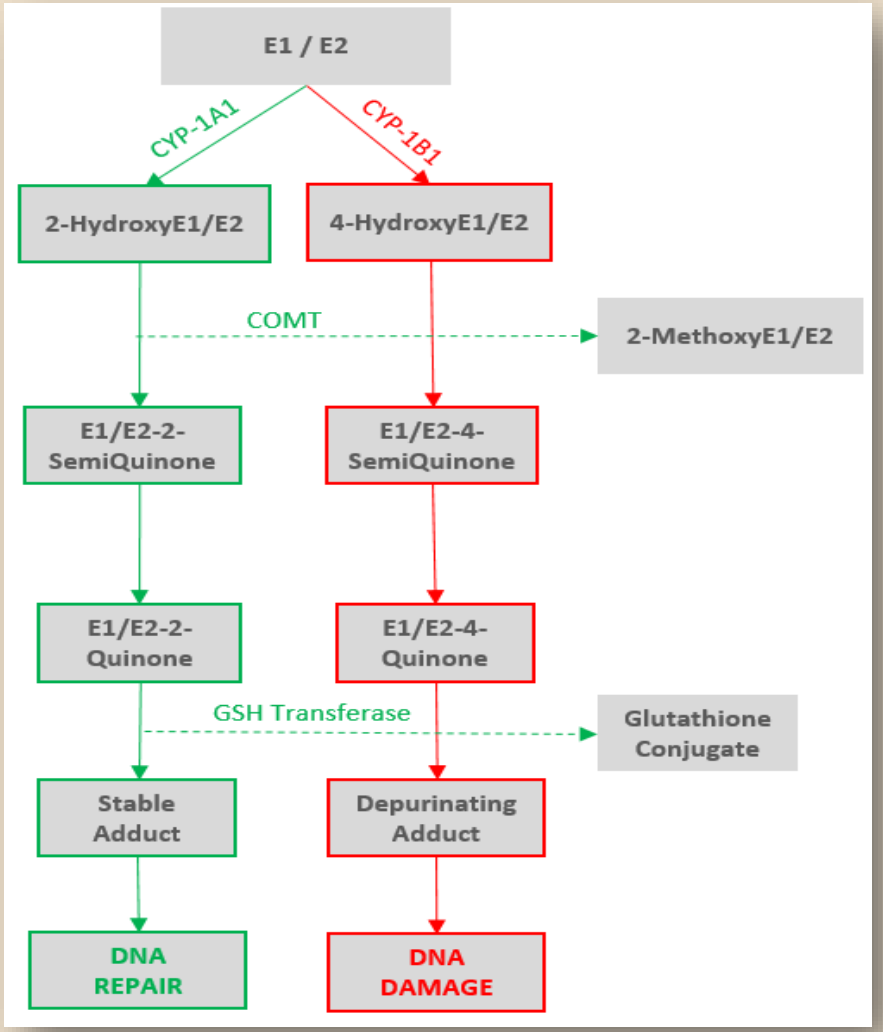
Preventing Negative Estrogen Burden

BIFIDOBACTERIUM significantly decreases glucuronidase activity[1].

CALCIUM-D-GLUCARATE is a potent beta-glucuronidase inhibitor that has been shown to exert anticarcinogenic effects[1].



1. Bouhnik et al., 1996
2. Walaszek et al., 1997

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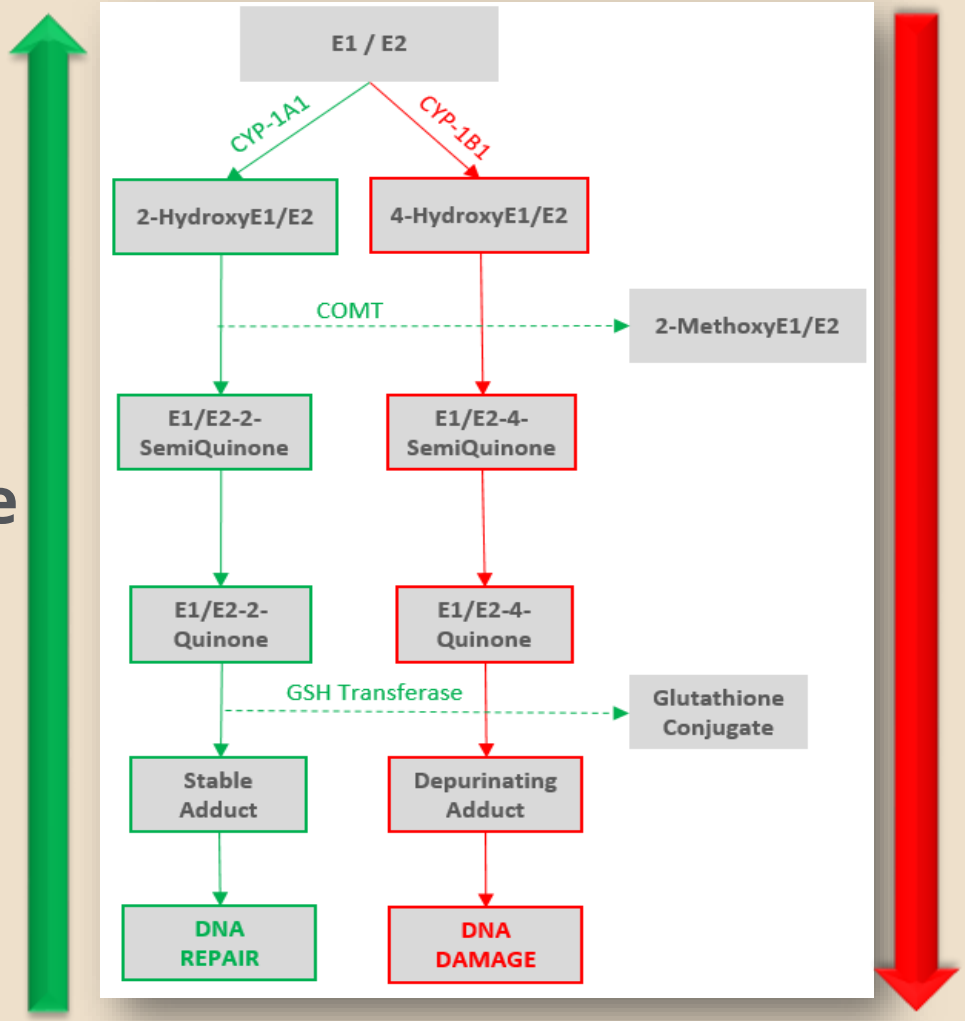
Preventing Negative Estrogen Burden

- Increase **CYP 1A1**
- Increase **COMT**
- Increase **quinone reductase**
- Increase **glutathione conjugation**



- Reduce **CYP-1B1**
- Reduce **Peroxidase**
- Decrease **β-glucuronidase** activity

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Which SNPs matter for Breast Cancer?

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MTHFR C677T

Genetic Polymorphisms

Treatment of MTHFR C677T

MTHFR C677T can be enhanced by treatment with folate and/or vitamin B12.

- E.g., In a study that assessed individuals with high dietary folate intake (>225 mcg/day), serum folate levels were significantly lower in individuals with 677TT that those with 677CC[1].
- Authors recommended that individuals homozygous for 677TT consume approximately 1.4 times more folate to reach levels seen in individuals with 677CC of 677TC genotypes[1].

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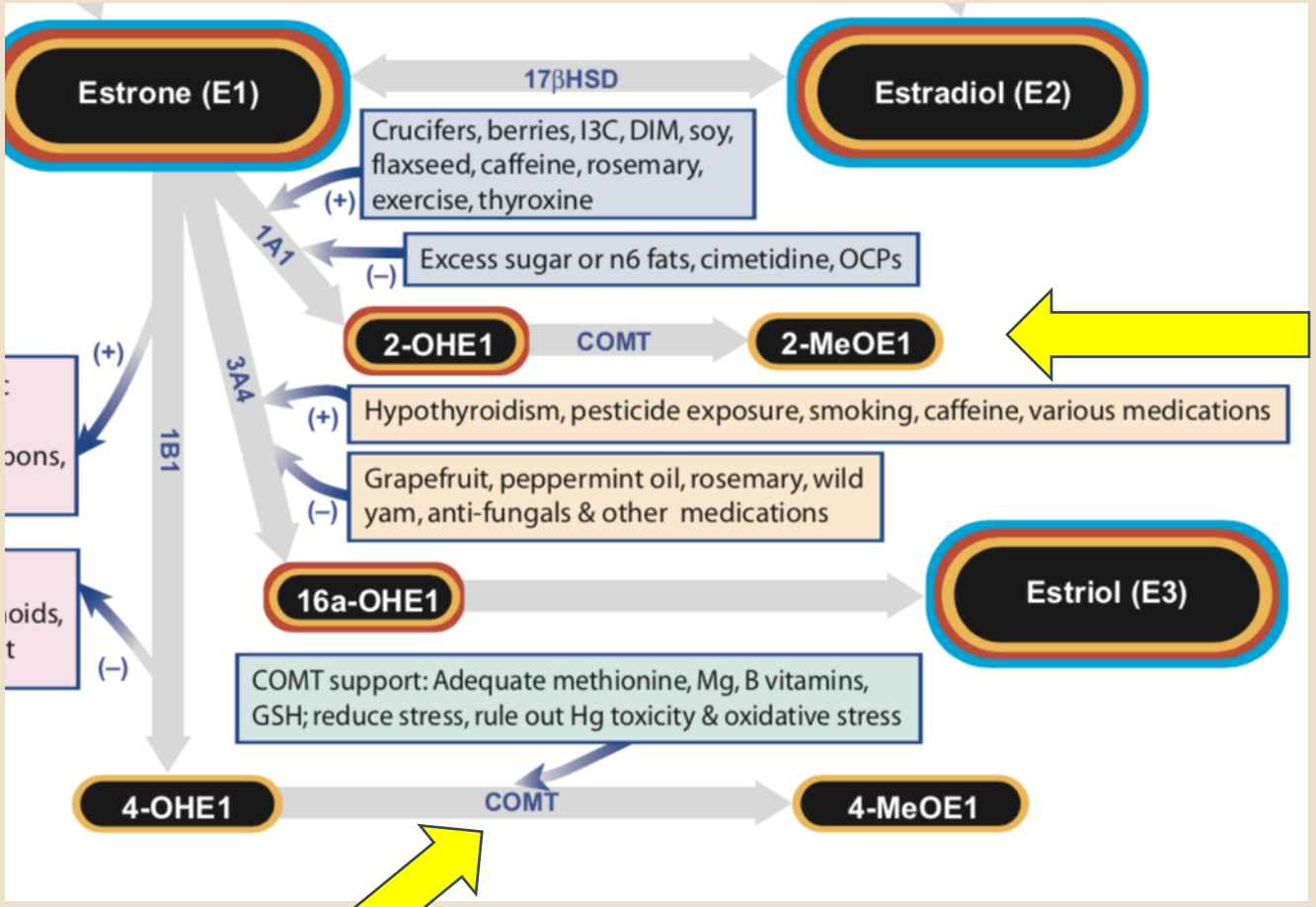
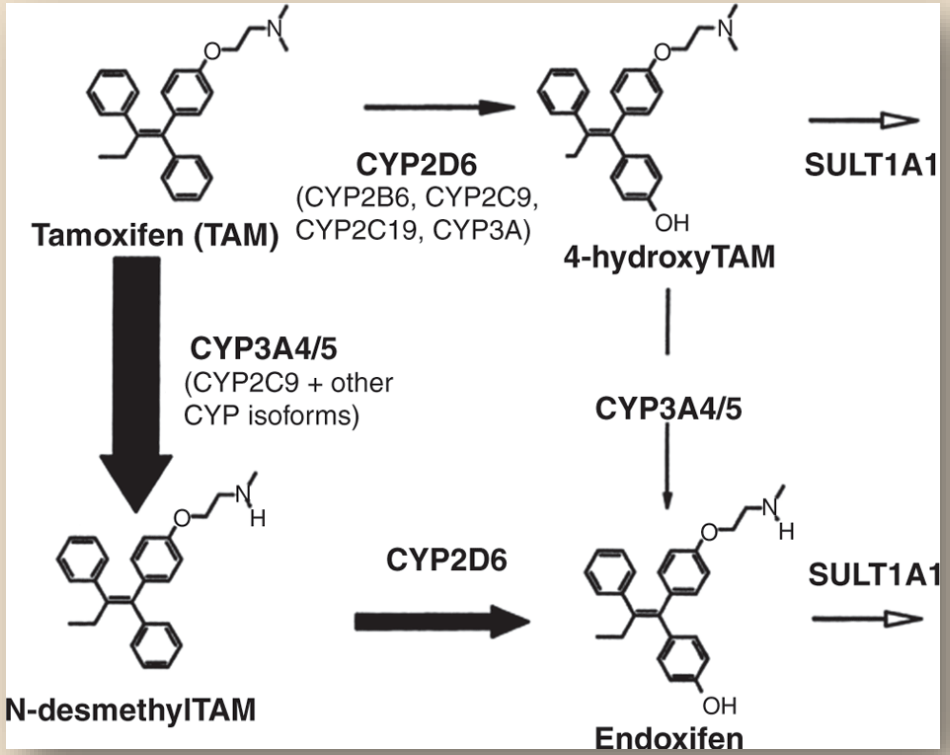
COMT

Genetic Polymorphisms



1. Kotyuk et al., 2015
2. Tan et al., 2016
3. Ashton et al., 2006

CYP 2D6

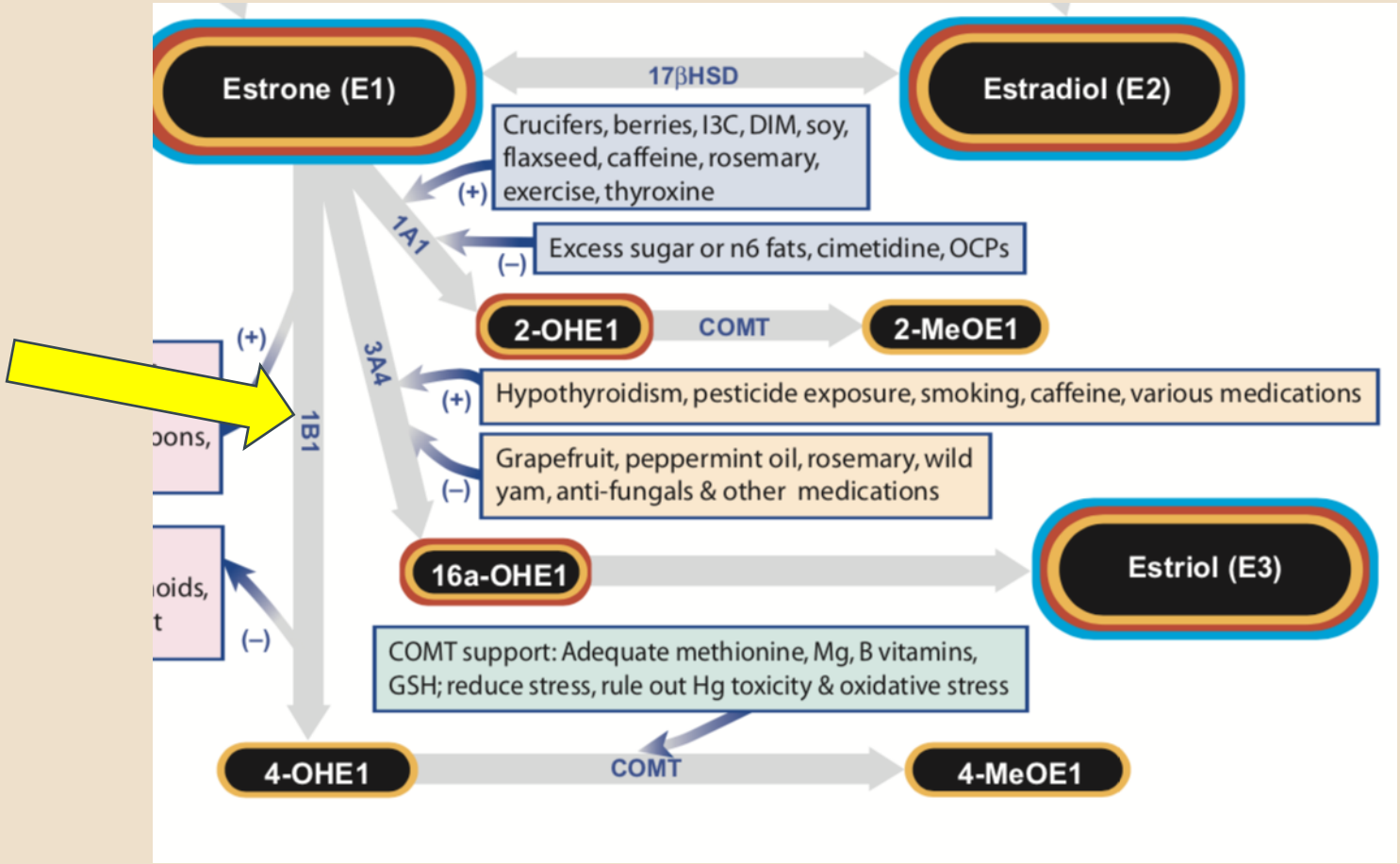


Genetics of CYP2D6

Genetic Type	CYP2D6 Activity	Ethnic Differences (Approximate)
Poor metabolizers	None	Caucasians 6%-10%
		Mexican Americans 3%-6%
		African Americans 2%-5%
		Asians ~1%
Intermediate metabolizers	Low	Not established
Extensive metabolizers	Normal	Most people are extensive metabolizers
Ultrarapid metabolizers	High	Finns and Danes 1%
		North Americans (white) 4%
		Greeks 10%
		Portuguese 10%
		Saudis 20%
		Ethiopians 30%

CYP 1B1

Metabolizes estrogen in 4 OH estrogens
If this is FAST, will increase the risk of estrogen dominance , especially if coupled with a slow COMT



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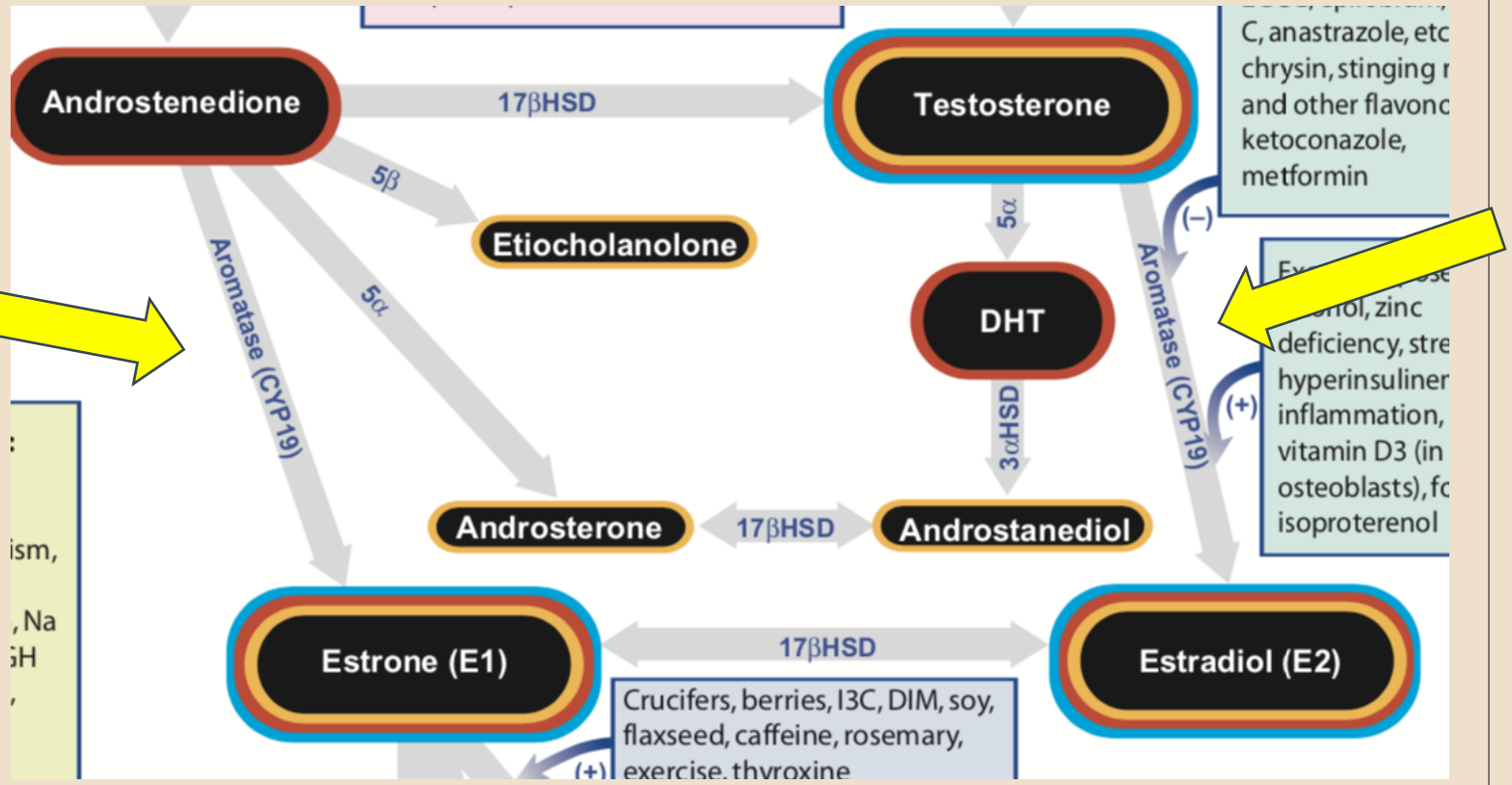
CYP 19A1

Converts Androgens (androstenedione and testosterone) into estrogens (estradiol and estrone)

If this is a fast version, it will make estrogen dominance worse



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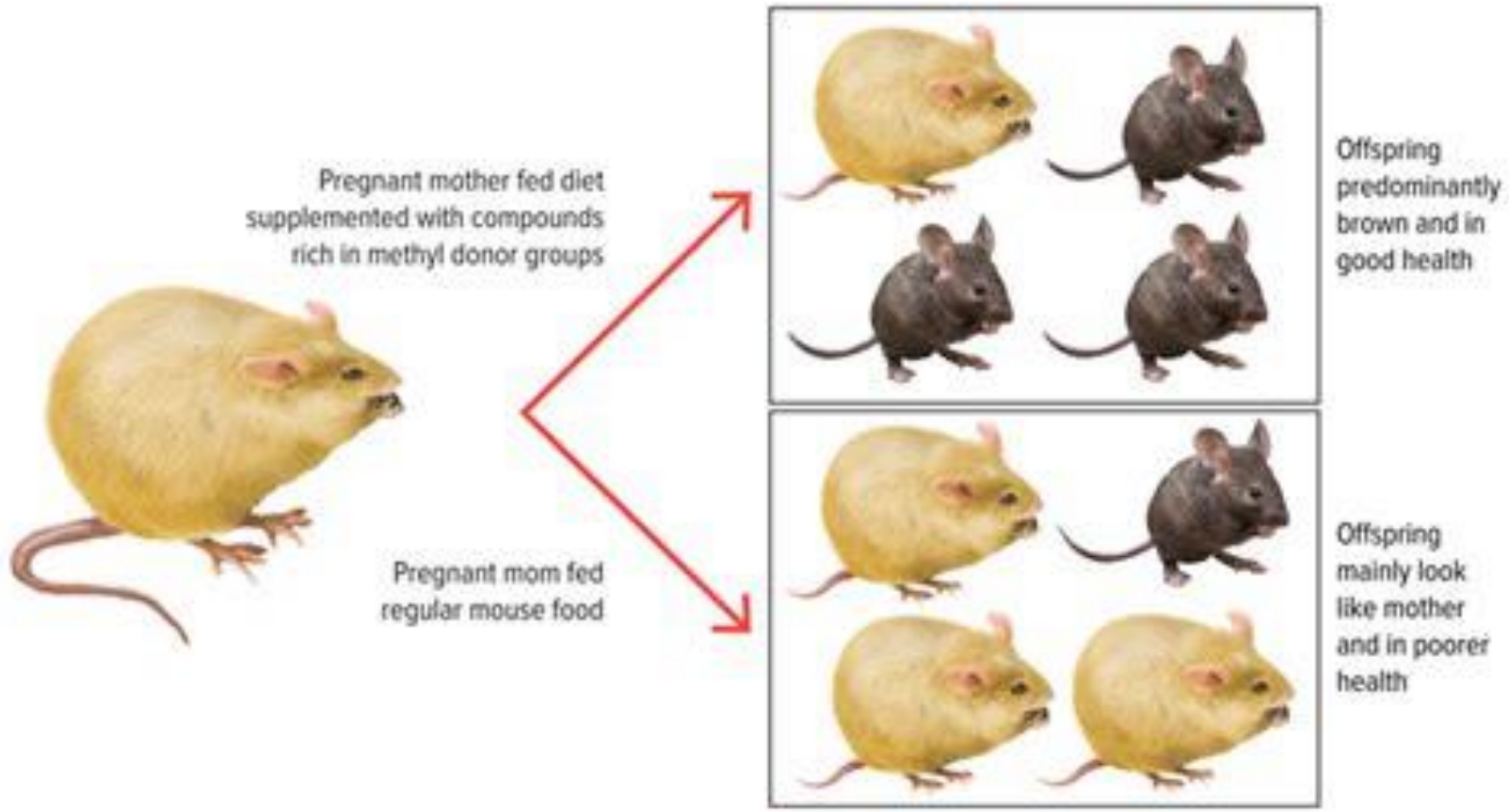
Epigenetics: Agouti Mice Experiment



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Starek-Siechowicz, Beata et al. “Endogenous estrogens-Breast cancer and chemoprevention” in Pharmacological Reports. (2021) 73:1497-1512.

- The high activity of CYP19 may increase breast cancer risk by providing more estrogen for activation to genotoxic metabolites and by stimulating breast epithelial cell mitosis.
- In a case–control study, the carriers of the CYP1B1*3 allele were significantly more frequent among breast cancer women, than those in the controls
- In a study of pre-menopausal women, a significantly higher risk for breast cancer with COMT(Met/Met) genotypes, compared with the homozygotes COMT(Val/Val) genotype women, was revealed.
- Increased levels of estrogen quinones and depurinating adducts occur when estrogen metabolism is unbalanced. This unbalanced metabolism is the result of overexpression of estrogen activating enzymes and/or deficiency of the deactivating enzymes
- The study has demonstrated that 4-OHE2 is the main estrogen metabolite responsible for induction of malignant phenotype cells.

Case 1
Part 1

Laura is a 32 yr old new patient that presents to you for hormone evaluation after recently being diagnosed with **breast cancer**. She had recently delivered a baby boy, and was diagnosed when he was 6 mo. old and she was still nursing. Her paternal aunt and paternal grandmother had a history of breast cancer. Her tumor was 2.5cm, Stage 2B, triple Negative receptors. She had BRAC testing, which was negative. She was told to get chemo every 2 weeks and get Lupron during that time.

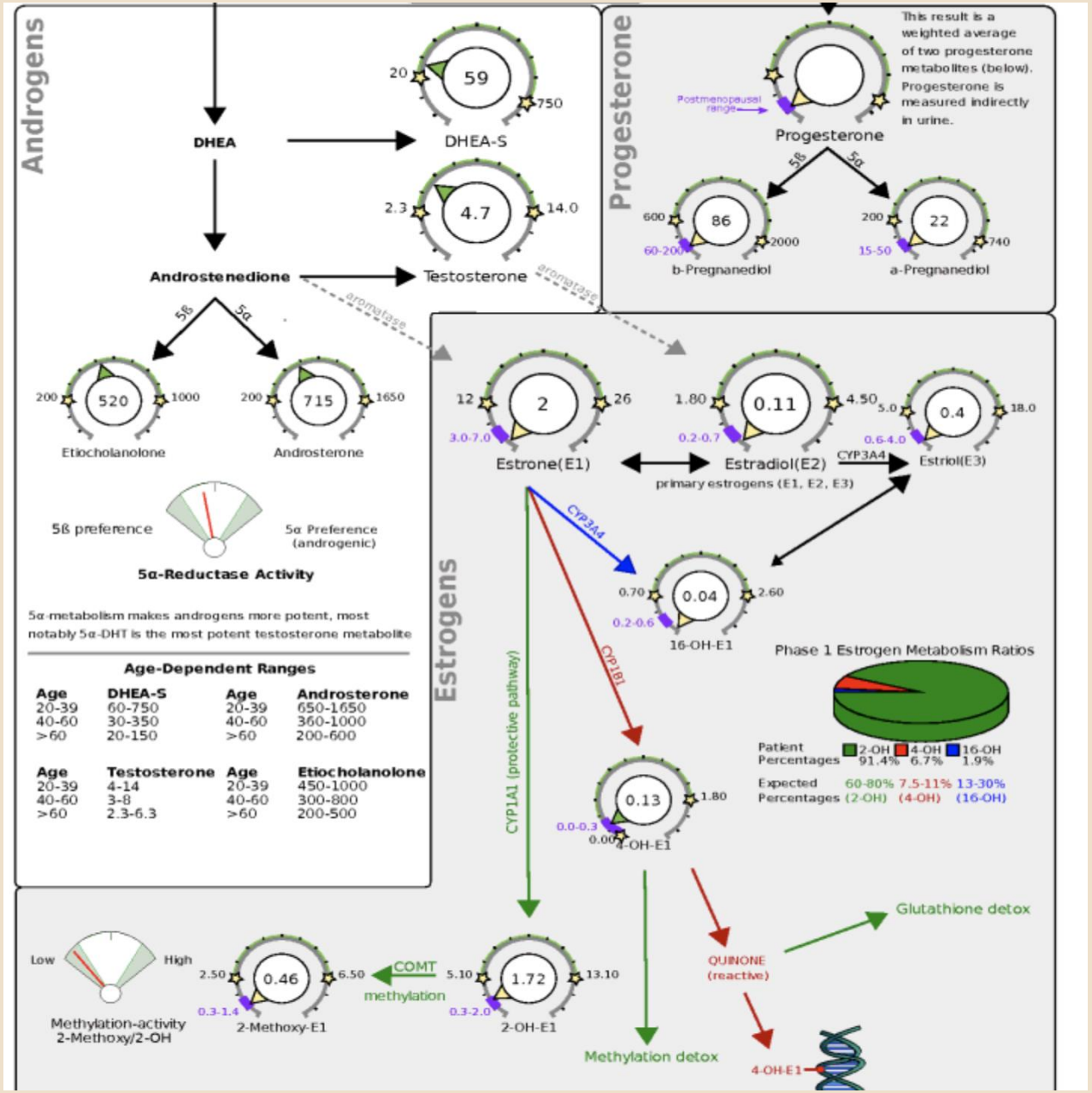
HORMONE GURU

Tara Scott, MD, FACOG, FAAFM, ABOIM, CNMP

Case 1
Part 1

- Vitamin D 63
- TSH 1.72
- Free T4 1.77
- HgBA1C 5.1
- Estradiol < 12
- FSH 7.4
- LH 1.1
- Progesterone 0.4
- DHEA 179
- Insulin 8
- Testosterone <80
- Estrone 9.5
- DHT 7

Urinary Hormone Results



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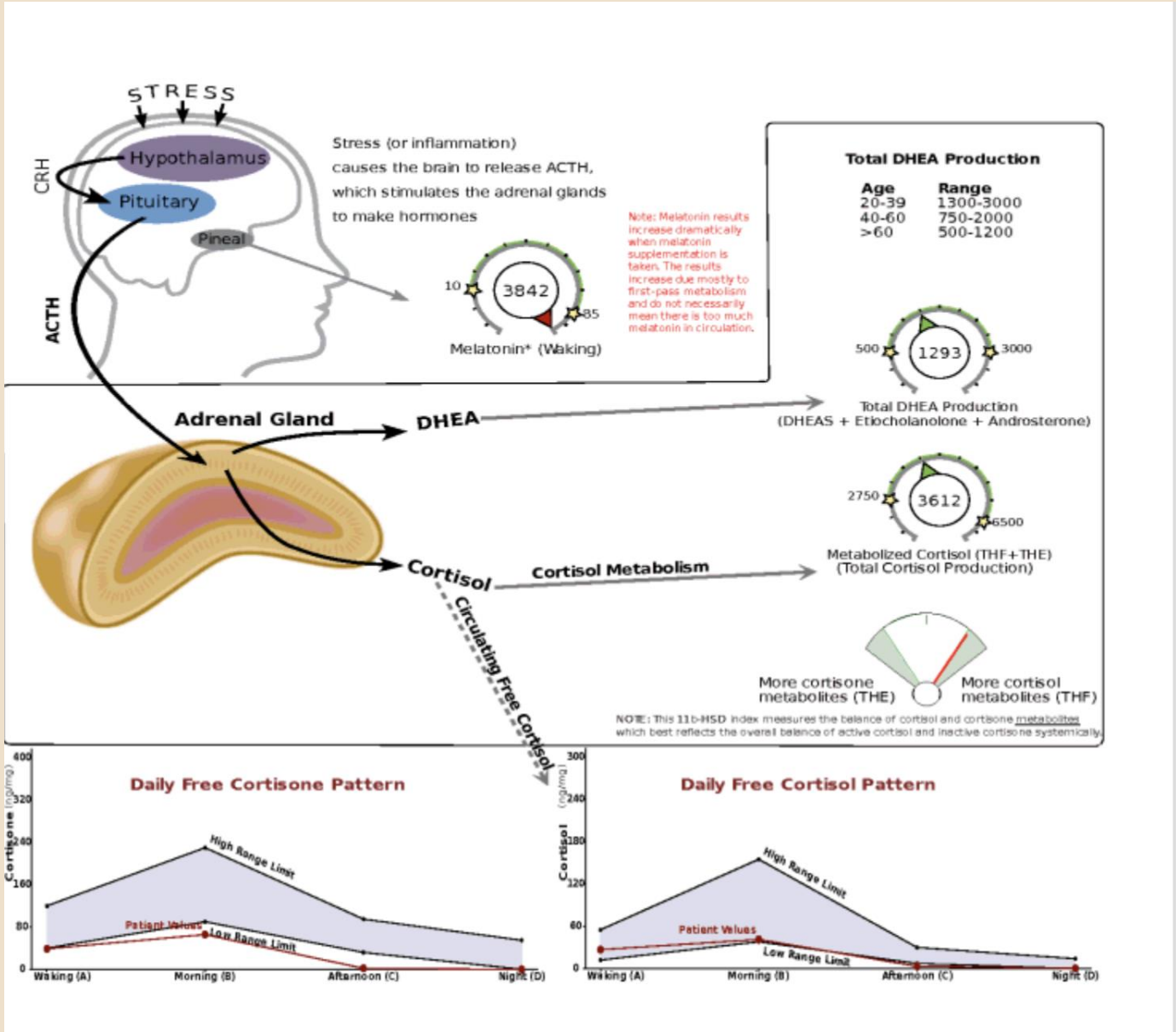
HORMONE GURU

Urinary Hormone Results



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HORMONE GURU

Genetic Test Results

GENE MTHFR

methylenetetrahydrofolate reductase

MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.

Position: p.Ala222Val, C677T | **SNP:** rs1801133

This C to T polymorphism results in the amino acid alanine being replaced with the amino acid valine. The valine containing T variant of the MTHFR enzyme has reduced activity.

Your Results	Genotype	Effect of Variant
CT	**CC** 56.9%*	Ancestral stability of the MTHFR enzyme and typical enzyme activity and rate of folate activation.
	CT 37.0%*	Mixed ancestral and reduced stability alleles for the MTHFR enzyme and intermediate rate of folate activation.
	TT 6.0%*	Decreased stability of the MTHFR enzyme and reduced enzyme activity and rate of folate activation.

* Population frequency

GENE MTHFR

methylenetetrahydrofolate reductase

MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.

Position: p.Glu429Ala, A1298C | **SNP:** rs1801131

This A to C polymorphism results in the amino acid glutamate being replaced with the amino acid alanine. The alanine containing C variant of the MTHFR enzyme is less stable and has lower activity.

Your Results	Genotype	Effect of Variant
AA	**AA** 56.3%*	Ancestral stability of the MTHFR enzyme and typical enzyme activity and rate of folate activation.
	AC 37.4%*	Mixed ancestral and reduced stability alleles for the MTHFR enzyme and intermediate rate of folate activation.
	CC 6.2%*	Decreased stability of the MTHFR enzyme and reduced enzyme activity and rate of folate activation.

GENE COMT

catechol-O-methyltransferase

COMT transfers a methyl group from S-adenosylmethionine (SAMe) to catecholamines.

Position: n.-1324A>G | **SNP:** rs6269

This G to A polymorphism causes a change in the regulatory sequence that decreases COMT activity by decreasing enzyme synthesis.

Your Results	Genotype	Effect of Variant
AA	**AA** 41.4%*	Reduced concentrations of COMT and higher catecholamine (dopamine, norepinephrine, and epinephrine) levels.
	AG 45.9%*	Mixed ancestral and reduced level alleles and intermediate concentrations of COMT and catecholamine (dopamine, norepinephrine, and epinephrine) levels.
	GG 12.7%*	Ancestral concentrations of COMT and lower catecholamine (dopamine, norepinephrine, and epinephrine) levels.

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HORMONE GURU

Case 2

Amy was first diagnosed with Breast cancer at age 31in 2009. She had a lumpectomy, chemo and radiation. She had a recurrence in the contralateral breast in 2011 and had bilateral mastectomies with reconstruction in 2012. She was on Tamoxifen and she continued to have heavy periods and hormonal symptoms.

HORMONE GURU
Tara Scott, MD, FACOG, FAAFM, ABOIM, CNMP

Estrogen Dominance

Saliva Results 2012

Gender: **Female** Phone: **330 208 6783** Height: **63 in**

Menopausal Status: **Pre-Menopausal - Irregular** Age: **35** DOB: **6/6/1977** Weight: **160 lbs**

Hormone Test	In Range	Out Of Range	Units	Range
Estradiol (saliva)	2.5		pg/ml	1.3-3.3 Premenopausal (Luteal)
Progesterone (saliva)		**20L**	**pg/ml**	**75-270 Premenopausal (Luteal)**
Ratio: Pg/E2 (saliva)		8L		Optimal: 100-500 when E2 1.3-3.3 pg/ml
Testosterone (saliva)	**34**		**pg/ml**	**16-55 (Age Dependent)**
DHEAS (saliva)	2.6		ng/ml	2-23 (Age Dependent)
Cortisol Morning (saliva)	**4.9**		**ng/ml**	**3.7-9.5**
Cortisol Night (saliva)	0.6		ng/ml	0.4-1.0

Current Hormone Therapies

None;

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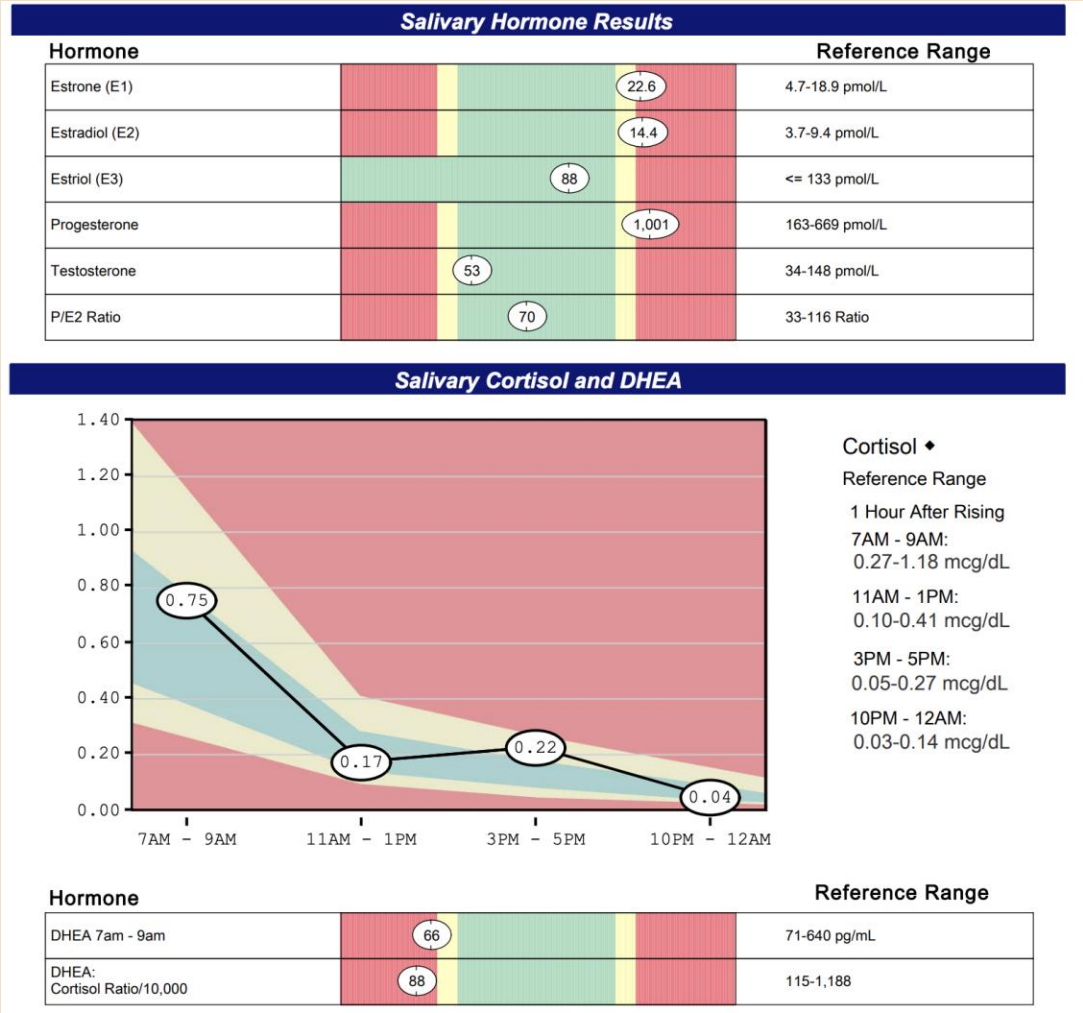
HORMONE GURU

Estrogen Dominance

Saliva Results 2013 on Tamoxifen



Salivary Hormone Results

Hormone	Value	Reference Range
Estrone (E1)	22.6	4.7-18.9 pmol/L
Estradiol (E2)	14.4	3.7-9.4 pmol/L
Estriol (E3)	88	<= 133 pmol/L
Progesterone	1,001	163-669 pmol/L
Testosterone	53	34-148 pmol/L
P/E2 Ratio	70	33-116 Ratio

Salivary Cortisol and DHEA

Hormone	Value	Reference Range
DHEA 7am - 9am	66	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	88	115-1,188

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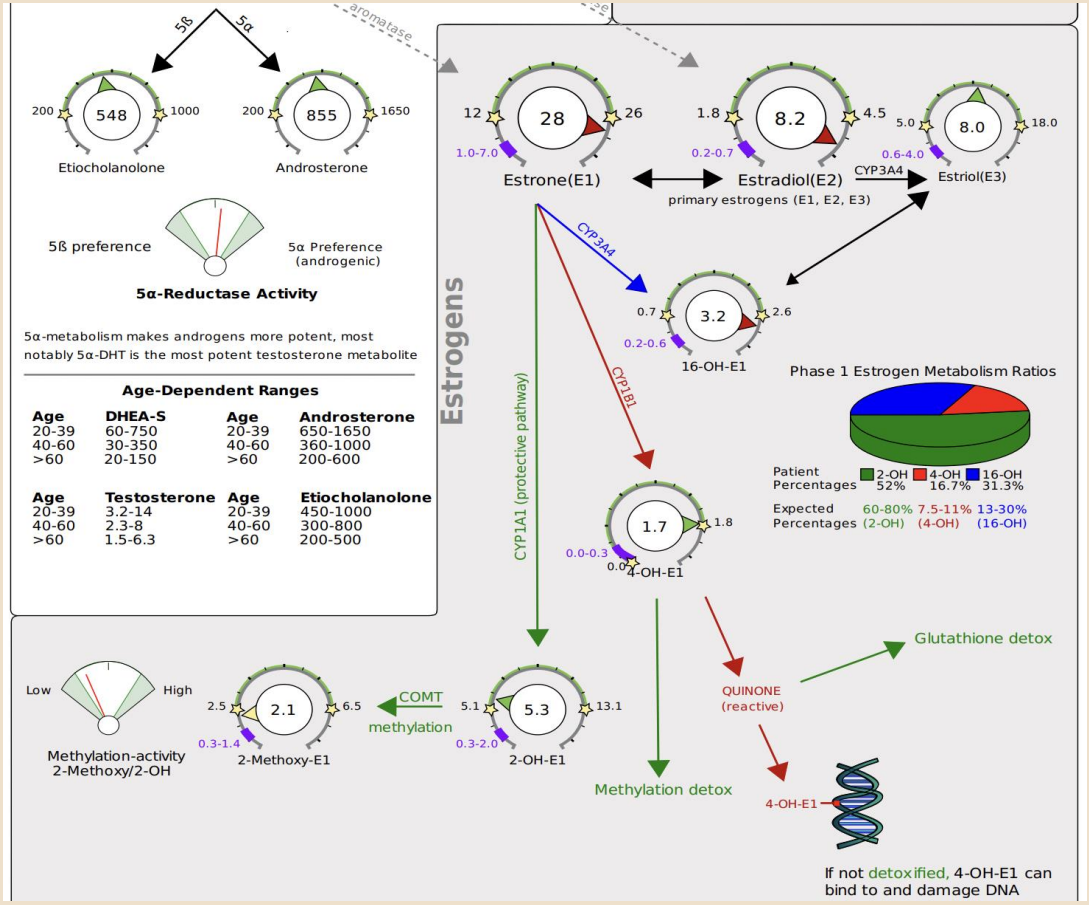
HORMONE GURU

Estrogen Metabolism Problems

Urine Results 2014 after Ovarian Cystectomy



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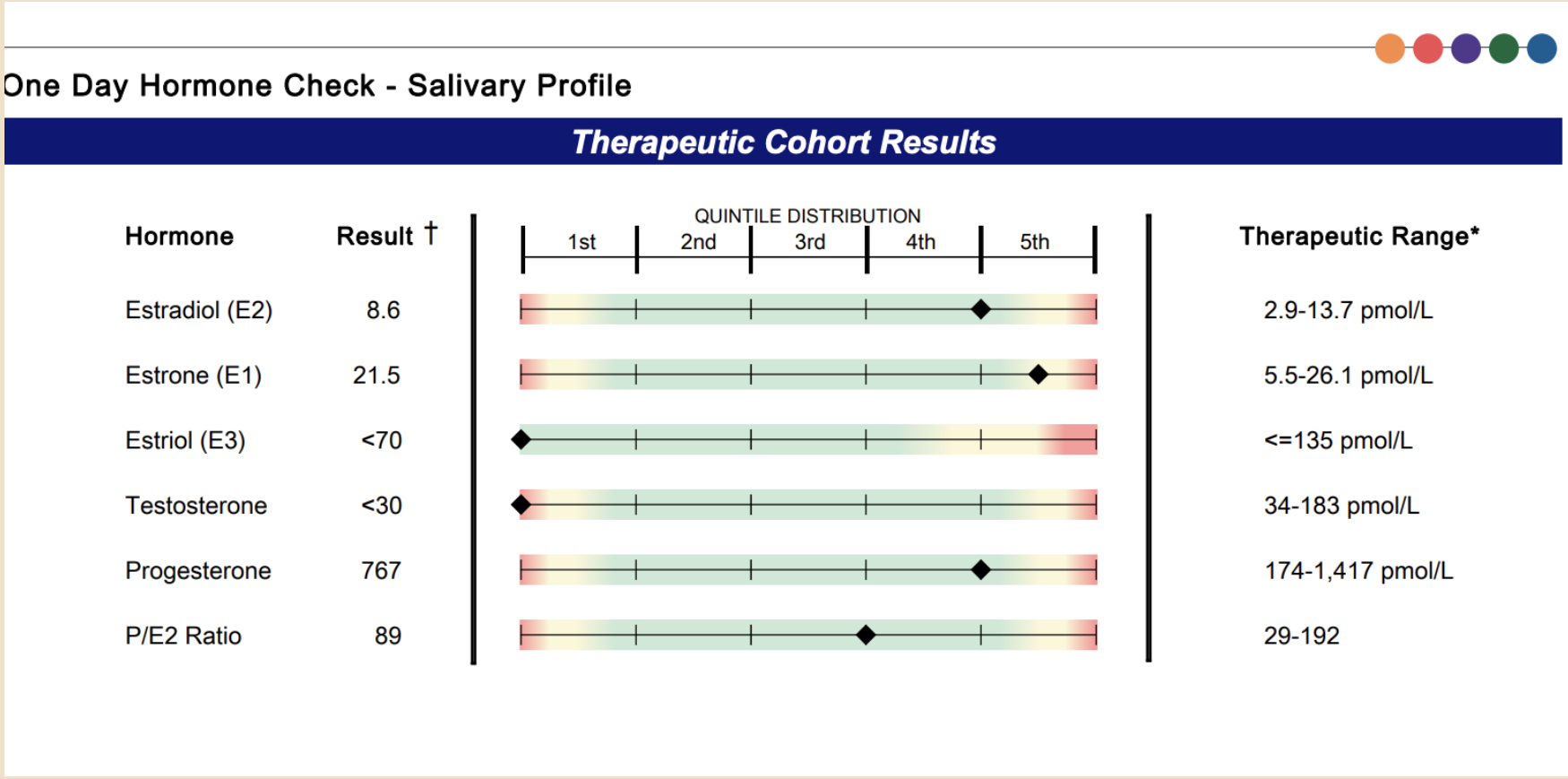
HORMONE GURU

Boothby, Lisa A., et Al. "Bio identical hormone therapy: a review" in *Menopause,* 2004, vol 11, No. 3, pp.356-367

	Estrogen Receptor-Alpha	Estrogen Receptor-Beta
17- Beta-estradiol	100	100
17- alpha-estradiol	58	11
Estriol	14	21
Estrone	60	37
4-OH-Estradiol	13	7
2-OH-Estrone	2	0.2
Tamoxifen	4	3
Raloxifene	69	16

Estrogen Metabolism Problems

Saliva Results 2016



One Day Hormone Check - Salivary Profile

Therapeutic Cohort Results

Hormone	Result †	QUINTILE DISTRIBUTION (1st 2nd 3rd 4th 5th)	Therapeutic Range*
Estradiol (E2)	8.6		2.9-13.7 pmol/L
Estrone (E1)	21.5		5.5-26.1 pmol/L
Estriol (E3)	<70		<=135 pmol/L
Testosterone	<30		34-183 pmol/L
Progesterone	767		174-1,417 pmol/L
P/E2 Ratio	89		29-192

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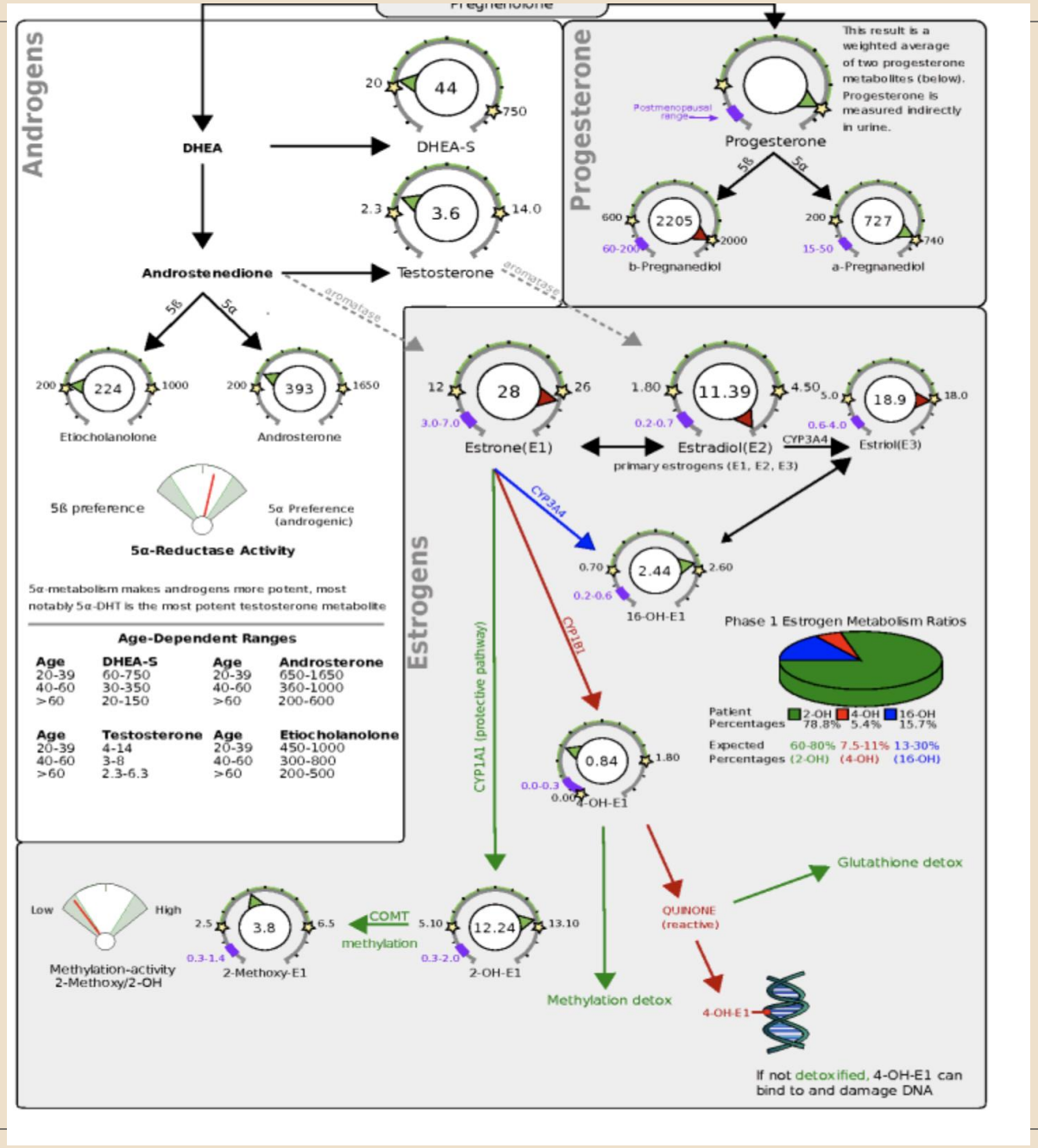
HORMONE GURU

Urine Results 2019



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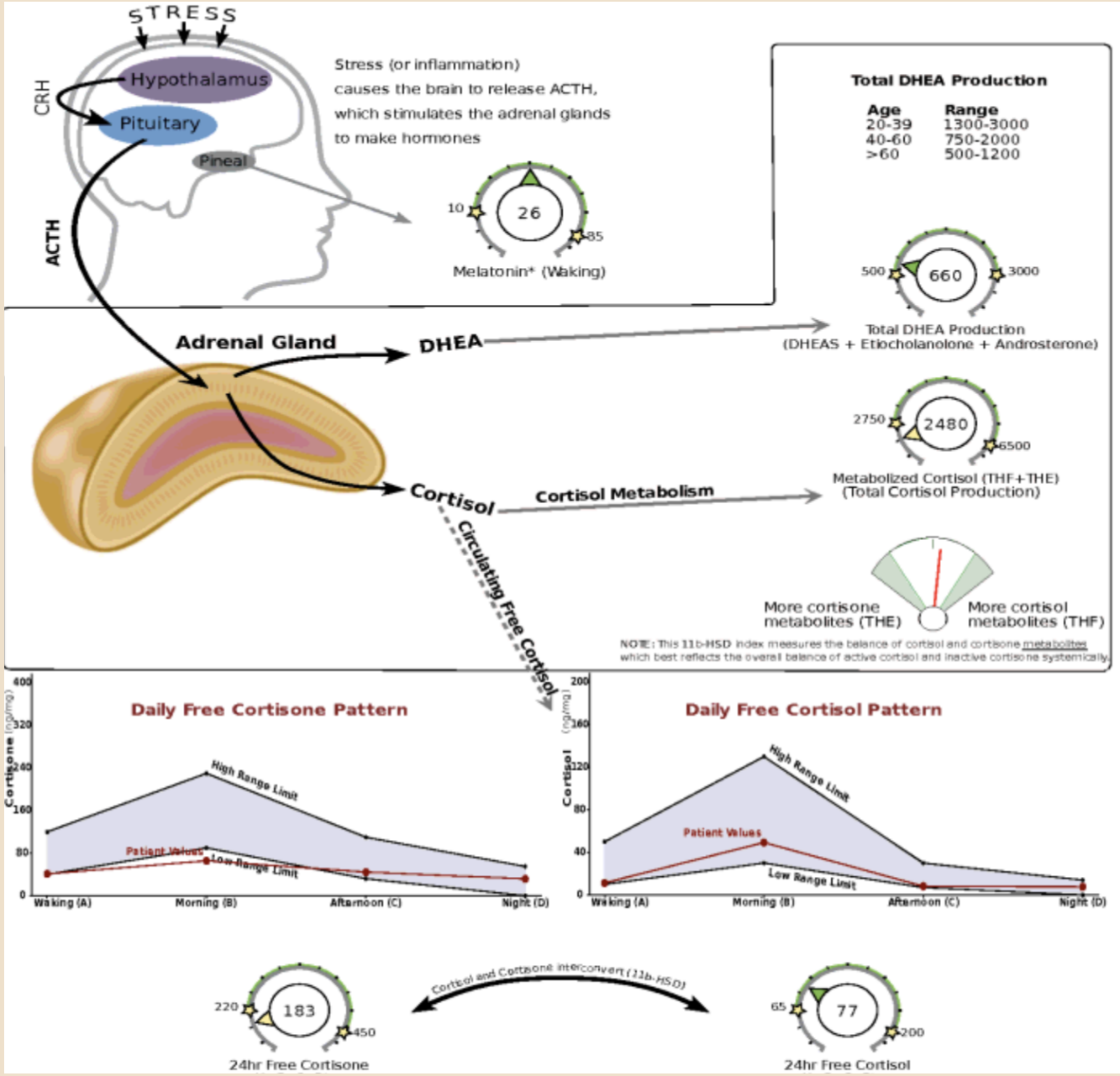
HORMONE GURU

Urine Results 2019



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HORMONE GURU

Does HRT contribute to or cause Breast Cancer???

HORMONE GURU

It All started in 2002 . . .

FINANCIAL REVIEW

Menopause drug scare hits women

600,000 women warned to stop combined HRT medication

Hormone alert for cance

True degree of therapy risk lost in the clamour of commentatc

More needed to settle HRT scare

Expert panel backs HRT cancer warning

HRT linked to cancer and stroke: doctors demand drug restrictions

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HORMONE GURU

(2002) WHI Study

- Premarin/ Prempro users- average age 63
- Risk for each 10,000 women
  - 7 Heart Attacks
  - 18 cases of blood clots in legs or lungs, mostly in first 2 yrs
  - 8 strokes
  - 8 breast cancers
  - 6 LESS cases of colon cancer
  - 6 LESS hip fractures
  - * 97.5% of women on treatment had no events

Why was the conclusion WRONG?

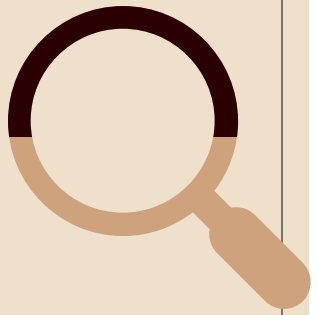
1) Older age/ preexisting disease
   - WHI and HERS I & II showed an increase in cardiac activity the first year
   - Early start is both heart protective and brain protective
2) Hormone preparation studied ratios and Progestin use
3) Oral route vs Transdermal shown in other studies to increase clotting factors and increase CRP
4) The difference between Progestin and Progesterone

(2010)
Follow-up to WHI

- JAMA, Oct. 20, 2010 - Follow up analysis of breast cancer mortality among those participants that had increased incidence in WHI

- Conclusion: "Estrogen plus progestin was associated with greater breast cancer incidence, and the cancers are more commonly node positive. Breast cancer mortality also appears to be increased with combined use of estrogen plus progestin."

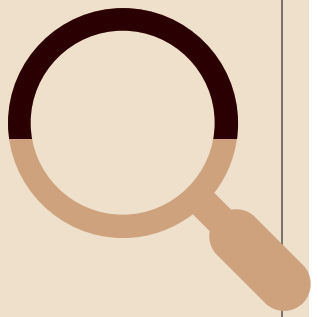
Follow-up to WHI



- **Estrogen Cuts Breast CA! Page 8**
- The Lancet Oncology, May 2012, Follow up of the E2 only arm of WHI- after 5-9 years of use.
- Incidence in E2- 0.27%
- Incidence in placebo- 0.35% per year

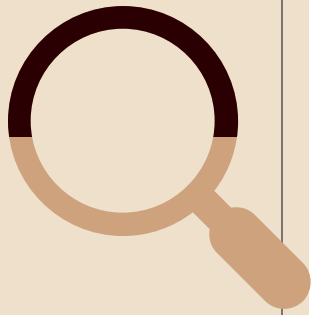
- **Estrogen-Only HT increases Breast CA risk - page 5**
- Nurses Health Study - 121,700 women ages 30-55
- 22% increased risk with 10-15 yrs use
- 43% increase for 15-19 years

(1995) Chang, K.J. et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertility and Sterility, 63,785-791.



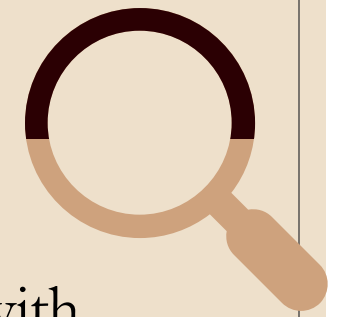
- "Adding progesterone to E2 significantly reduced the proliferative effect of E2 alone. The present data shows that in vivo, 10to 13 days of P exposure decreases the growth fraction of normal epithelial cells in the breast of premenopausal women."
- "It also suggests that P or related drugs may have a therapeutic value to prevent breast epithelial hyperplasia when used > 10 days per month at approximate substitutive doses."

(2002) Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women de Lignières B, Climacteric. 2002 Dec;5(4):332-40



- 83% were receiving exclusively or mostly a combination of a transdermal estradiol gel and a progestin other than MPA
- Most using transdermal estradiol and micronized progesterone (common practice in France)
- "We were unable to detect an increase in the relative risk (RR) of breast cancer (RR 0.98, 95% confidence interval (CI): 0.65-1.5) in the HRT users"

(2005) Progestins and progesterone in hormone replacement therapy and the risk of breast cancer, Campagnoli, C. et al, . Journal of Steroid Biochemistry & Molecular Biology, 96,95-108.

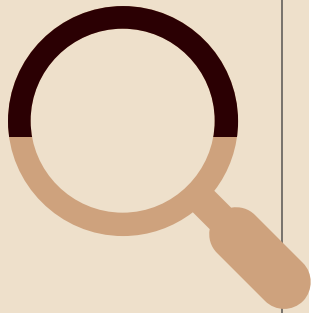


- "The incidence of BC (breast cancer) is two-to-three times greater in women with serum levels of estradiol or testosterone in the higher quartiles or quintiles of the distribution."
- "In this study, oral micronized progesterone, contrarily to synthetic progestins, did not increase BC risk in women treated with transdermal estradiol."
- "A key metabolic alteration that increases BC risk is the resistance to insulin action on carbohydrates (insulin resistance: reduced insulin sensitivity), due to genetic and nutritional factors, with consequent hyperinsulinemia."

(2005) Progestins and progesterone in hormone replacement therapy and the risk of breast cancer

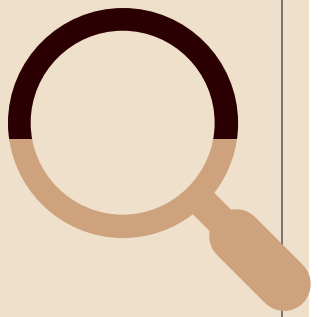
- "High levels of free testosterone have been identified as a risk factor for BC both before and after menopause."
- "Estrogens, particularly orally administered estrogens, are able to counteract metabolic factors that increase the risk of BC. One way they do this is by increasing insulin sensitivity and hence lowering circulating insulin levels."
- "We therefore suggest that when HRT is indicated, preparations containing progesterone and not a synthetic progestin should be used, according to a sequential or cyclic-combined regimen. In this way the risk of endometrial cancer is minimized without increasing the risk of BC"

(2005) E3N-EPIC Cohort



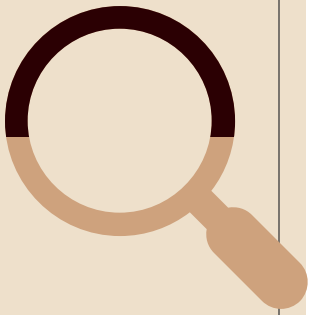
- Almost 55,000 women on HRT, examined relative risk of estrogen alone, estrogen plus progestin, or estrogen plus micronized progesterone.
- "The association between HRT use and breast cancer risk most likely varies according to the type of progestin used. There was no or little increase in risk with estrogens used alone or combined with micronized progesterone."
- "Our study confirms previous findings of an increase in invasive breast cancer risk with estrogens combined with synthetic progestins compared to no HRT use"

(2008) E3N-EPIC Cohort



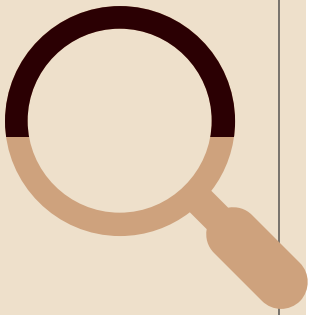
- Follow up published in Jan 2008
- 80,377 postmenopausal women ages 40-65 years, followed for 8.1 years
- CEE were only used by 1.3%- almost exclusively used forms of transdermal E2
- RR for Breast CA- E2 only 1.29
  - E2 + progestin 1.69
  - E2 + micro. Pg 1.00
  - NO HRT 1.00

(2009) The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? Holtorf, K, Postgraduate Medicine, 121,1-13.2009



- "Synthetic progestins have potential anti-apoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation. In contrast, progesterone inhibits estrogen-stimulated breast epithelial cells. Progesterone also downregulates estrogen receptor-1 in the breast, induces breast cancer cell apoptosis, diminishes breast cell mitotic activity, and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1."

(2009) The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? Holtorf, K, Postgraduate Medicine, 121,1-13.2009

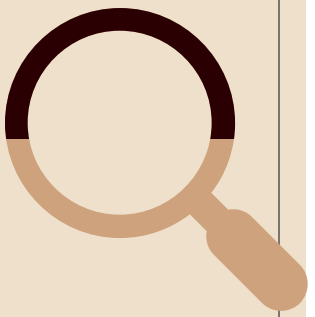


- "Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens, potentially contributing to their carcinogenic effects, which are not apparent with progesterone."
- "Use of unopposed postmenopausal estrogen from ages 50-60 years increased the risk for breast cancer to age 70 by 23 %."

(2012) Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: Extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Anderson, G.L. et al, Lancet Oncology, 13, 476–486

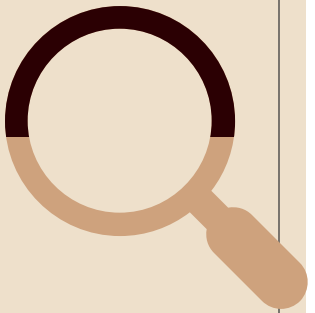
- "Elevated concentrations of endogenous oestrogen have been consistently associated with increased risk of breast cancer. Exogenous oestrogen use has also been associated with higher breast cancer incidence in many but not all observational studies, especially in leaner women and those receiving oestrogen long term. Oestrogen use has been linked to hormone-receptor positive and early stage disease, suggesting a better prognosis, although associations with breast cancer mortality are mixed."
- "Between 1993 and 1998, the WHI enrolled 10739 postmenopausal women from 40 US clinical centers into a randomised, double-masked, placebo-controlled trial. Women aged 50-79 who had undergone hysterectomy and had expected 3-year survival and mammography clearance were randomly allocated by a computerised, permuted block algorithm, stratified by age group and centre, to receive oral conjugated equine oestrogen (0.625 mg per day; n=5310) or matched placebo (n=5429)."
- "After a median follow-up of 8 years, the use of oestrogen for a median of 5-9 years was associated with lower incidence of invasive breast cancer (151 cases, 0-27% per year) compared with placebo."

(2014) Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort, Fournier, Breast Cancer Res Treat. 2014; 145(2): 535–543



- We found that long-term (>5 years) use of EPT containing progestagens other than progesterone or dydrogesterone was associated with significant increases in risk, even many years after treatment cessation
- Our study further suggests that long-term use of estrogen-only can be associated with an increased breast cancer risk more than 10 years after treatment cessation,

(2016) Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis, Asi et al. Systematic Reviews (2016) 5:121

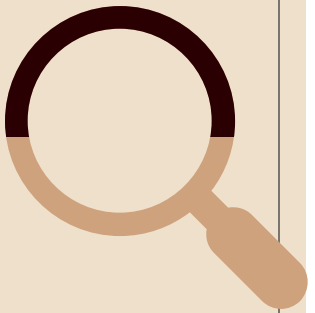


- We included two cohort studies and one population-based case-control study out of 3410 citations identified by the search. The included studies enrolled 86,881 postmenopausal women with mean age of 59 years and follow-up range from 3 to 20 years
- Progesterone was associated with lower breast cancer risk compared to synthetic progestins when each is given in combination with estrogen, relative risk 0.67; 95 % confidence interval 0.55–0.81.

(2017) Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: a systematic review and meta-analysis, Gynecol Endocrinol. 2017 Feb;33(2):87-92. doi: 10.1080/09513590.2016.1248932. Epub 2016 Nov 29.

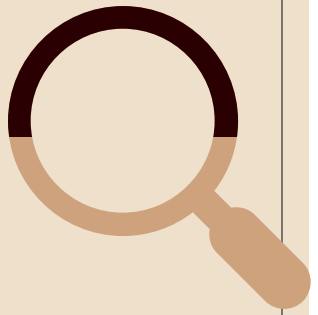
- A total of 14 studies were included in our study. In estradiol-only therapy analysis, meta-analysis resulted a pooled OR =0.90, 95% CI (0.40, 2.02) from the RCTs and pooled OR = 1.11, 95% CI (0.98, 1.27) from observational studies. However, in the analysis of estradiol-progestogen therapy, the risk of breast cancer varies according to the type of progestogen and the duration with more than five years (OR = 2.43, 95% CI (1.79, 3.29)) presented a higher risk than using less than five years (OR = 1.49, 95% CI (1.03, 2.15)).

(2018) The impact of micronized progesterone on breast cancer risk: a systematic review, CLIMACTERIC, 2018 VOL. 21, NO. 2, 111–122



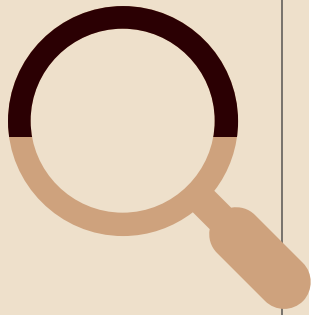
- Estrogens combined with oral (approved) or vaginal (off-label use) micronized progesterone do not increase breast cancer risk for up to 5 years of treatment duration;
- There is limited evidence that estrogens combined with oral micronized progesterone applied for more than 5 years are associated with an increased breast cancer risk; and
- Counseling on combined MHT should cover breast cancer risk – regardless of the progestogen chosen.

(2019) The clinical characteristics and prognosis of endometrial carcinomas that occur after breast cancer: does hormone receptor status of breast cancer matter?, Arch Gynecol Obstet. 2019 Oct 1. doi: 10.1007/s00404-019-05318-2.



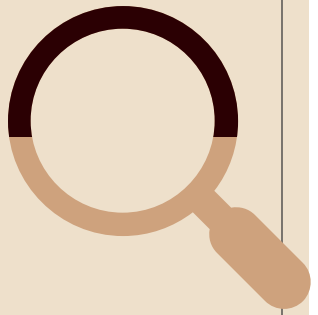
- Compared to the general population, the incidence of EC (endometrial cancer) in patients with breast cancer was increased markedly. Patients with EC following ER+ or HR- breast cancer shared the same clinicopathological features and prognoses. All patients need close monitoring regardless of breast cancer hormone receptor status.
- This emphasizes the SIMILARITY of the BREAST and UTERINE cell

(2019) Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet- Sept 2019



- During prospective follow-up, 108 647 postmenopausal women developed breast cancer at mean age 65 years (SD 7); 55 575 (51%) had used MHT. Among women with complete information, mean MHT duration was 10 years (SD 6) in current users and 7 years (SD 6) in past users,
- If these associations are largely causal, then for women of average weight in developed countries, 5 years of MHT, starting at age 50 years, would increase breast cancer incidence at ages 50–69 years by about one in every 50 users of oestrogen plus daily progestogen preparations; one in every 70 users of oestrogen plus intermittent progestogen preparations; and one in every 200 users of oestrogen-only preparations. The corresponding excesses from 10 years of MHT would be about twice as great

(2019) Hormone therapy study restokes debate over breast cancer risk, CMAJ September 30, 2019 191 (39) E1088-E1089; DOI: https://doi.org/10.1503/cmaj.1095815



- According to the International Menopause Society and the British Menopause Society, most of the data in the *Lancet* paper are from older observational studies of formulations and doses of hormone therapy that are no longer recommended.

Breast Cancer

- The risk of breast cancer related to hormone therapy use is low, with estimates indicating a rare occurrence (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with conjugated equine estrogens plus medroxyprogesterone acetate). (Level I)
- Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors. (Level III)
- The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen, prior exposure, and individual characteristics. (Level II)
- Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation. (Level II)

Breast Cancer (cont)

- A preponderance of data does not show an additive effect of underlying breast cancer risk and hormone therapy use on breast cancer incidence. (Level II)
- Insufficient data are available to assess the risk of breast cancer with newer therapies such as tissue-selective estrogen complexes, including bazedoxifene plus conjugated equine estrogens. (Level II)
- Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history or after bilateral salpingo-oophorectomy for *BRCA 1* or *2* genetic variants. (Level II)

BREAST CANCER (CONT)

- Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe vasomotor symptoms unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. (Level III)
- For survivors of breast cancer with the genitourinary syndrome of menopause, low-dose vaginal estrogen therapy (ET) or dehydroepiandrosterone may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal ET for women on aromatase inhibitors. (Level III)
- Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. (Level I)

BREAST CANCER (CONT)

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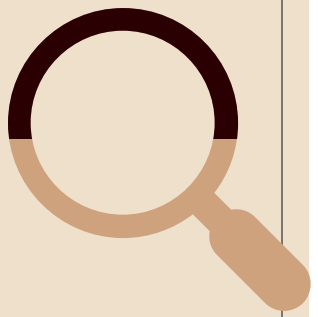
(2022) Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study

- Included longitudinal data from a national cohort of postmenopausal women, diagnosed 1997-2004 with early-stage invasive estrogen receptor–positive nonmetastatic BC, who received no treatment or 5 years of adjuvant endocrine therapy
- Among 8461 women who had not received VET((vaginal therapy) or MHT apy) (systemic menopausal hormone therapy) before BC diagnosis, 1957 and 133 used VET and MHT, respectively, after diagnosis. Median follow up was 9.8 years for recurrence and 15.2 years for mortality
- ***In postmenopausal women treated for early-stage estrogen receptor–positive BC, neither VET nor MHT was associated with increased risk of recurrence or mortality***. A subgroup analysis revealed an increased risk of recurrence, but not mortality, in patients receiving VET with adjuvant aromatase inhibitors.

Do hormone levels matter after Breast Cancer diagnosis?

Hankinson, Susan E and A. Heather Eliassen "Circulating Sex Steroids and breast cancer risk in premenopausal women" in Horm Cancer. 2010 February; 1(10): 2-10



- Follicular, but not luteal, total and free estradiol were significantly associated with breast cancer risk
- To date there have been only three prospective studies to evaluate estrogen metabolites and breast cancer risk among premenopausal women, and these studies only have included the 2- hydroxyestrone and 16α-hydroxyestrone metabolites
- In the large EPIC cohort study, with 285 cases and 555 controls, a significant inverse association was observed between progesterone levels (residuals from spline regression model) and breast cancer risk
- The only consistent finding to date is a positive association between testosterone levels and risk of invasive breast cancer in premenopausal women

Fortner, Renee et al, "Premenopausal endogenous steroid hormones and breast cancer risks: results from the Nurses' Health Study II" in Breast Cancer Research. 2013. 15:R19, 1-11.

- 29611 participants: 18521 provided early follicular and mid luteal
- 634 premenopausal women developed breast cancer- matched for 1264 controls
- No association between follicular estradiol, estrone, and free estradiol and risk of either total or invasive breast cancer
- Luteal estradiol was positively associated with ER+
- Luteal estrone, free Estradiol and progesterone were not associated with risk
- Androgens were associated with modestly increased risk of breast cancer, stronger for invasive ER+/PR+ disease

Kaakas, Rudolf et al. "Premenopausal serum sex hormone levels in relation to breast cancer risk, overall and by hormone receptor status- Results from the EPIC cohort" in Int. J. Cancer. 143, 1947-1957 (2014)

- Case-control study in European Prospective Investigation into Cancer and Nutrition (EPIC cohort)- 801 breast cancer cases and 1132 matched control subjects
- Analyzed prediagnostic serum estradiol, free estradiol, progesterone, testosterone, free testosterone and SHBG.
- Higher premenopausal circulating testosterone levels are associated with an increased risk of developing breast cancer, but do not show a significant association of estradiol or progesterone with breast cancer risk overall, by menstrual cycle phase or by tumor receptor status, although a possible risk increase with higher estradiol levels for tumors diagnosed before age 50

Key, et al. "Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies" J Natl Cancer Inst. 2002 Apr 17;94(8):606-16.

- Analyzed the individual data from nine prospective studies on 663 women who developed breast cancer and 1765 women who did not. None of the women was taking exogenous sex hormones when their blood was collected to determine hormone levels.
- The risk for breast cancer increased statistically significantly with increasing concentrations of all sex hormones examined: total estradiol, free estradiol, non-sex hormone-binding globulin (SHBG)-bound estradiol (which comprises free and albumin-bound estradiol), estrone, estrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone.
- The increases in risk associated with increased levels of all sex hormones remained after subjects who were diagnosed with breast cancer within 2 years of blood collection were excluded from the analysis.

Key, et al. "Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies" J Natl Cancer Inst. 2002 Apr 17;94(8):606-16.- CONTINUED

- The main finding of our study was that postmenopausal women with relatively high serum concentrations of sex hormones had a roughly twofold higher risk for breast cancer than did postmenopausal women with relatively low serum concentrations of sex hormones
- Levels of estrone and estrone sulfate were also strongly associated with breast cancer risk, but it was not possible to say whether this is because they are converted into estradiol, because they are correlated with estradiol levels or, in the case of estrone, because of a direct biologic effect on breast cells.
- One limitation of our study is that the RRs we calculated are all based on single measurements of serum hormone concentrations for each woman.
- This pooled analysis of the worldwide data from prospective studies has established that serum concentrations of endogenous sex hormones are strongly associated with breast cancer risk in postmenopausal women
- In the future, the measurement of endogenous hormone levels might help to identify those women who are at increased risk for breast cancer.

Luo, Yang, et al "Combination of Endogenous Estradiol and Adipokine Leptin in Breast Cancer Risk and Prognosis Assessment in Postmenopausal Chinese Women" in Front Endocrinol (Lausanne). 2021 Dec 14;12:76646

- A total of 182 postmenopausal breast cancer patients and 111 healthy subjects from January 2010 to August 2010 were included in the analysis
- The level of estradiol was significantly higher ($P<0.001$) but the level of leptin had no significant difference ($P = 0.764$) in postmenopausal breast cancer patients compared with healthy subjects.
- In postmenopausal women, the breast cancer risk is significantly elevated with higher levels of total and free E2
- In postmenopausal women, adipose tissue becomes the main producer of E2 through the enzymatic conversion of androgen precursors to E2 carried out by aromatase (9). In obese women, the elevated aromatase levels led to an increase of E2, resulting in poorer treatment effects and inferior prognosis in breast cancer
- In summary, our study suggested that circulating E2 played an important role in breast cancer etiology and was associated with increased risk even in low-estrogen nations with independent expression of ER status.

Zhang, Xuehong, "Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up" in Breast Cancer Res Treat. 2013 Feb; 137(3): 883–892.

- nested case-control analyses within the Nurses' Health Study. Blood samples were collected in 1989-1990 and again in 2000-2002
- Circulating steroid hormone levels were statistically significantly higher among cases than controls for all hormones investigated, except SHBG, where higher levels were observed among control
- Compared to the lowest quartile, the highest quartile of pre-diagnostic levels of estradiol, free estradiol, DHEAS, testosterone and free testosterone was significantly associated with a 1.4-2.0-fold increased breast cancer risk, the associations were similar whether the hormones were measured within 10 years or 10-20 years before diagnosis
- Our current study further supports that a single blood sex hormone measurement can predict breast cancer risk for up to16- 20 years prior to breast cancer diagnosis, with statistically significant positive associations observed for estradiol, free estradiol, testosterone, free testosterone, and DHEAS, and a significant inverse association with SHBG.

Eliassen, A. Heather, et al "Urinary estrogens and estrogen metabolites and subsequent risk of breast cancer among premenopausal women" in Cancer Res. 2012 February 1: 72 (3) : 696-706

- Examined 15 urinary estrogens/estrogen metabolites (EM) and breast cancer risk among premenopausal women in a case-control study nested within the Nurses' Health Study II (NHSII). In 1996–1999, urine was collected from 18,521 women during the mid-luteal menstrual phase. Breast cancer cases (N=247) diagnosed between collection and June 2005 were matched to 2 controls each (N=485).
- Higher urinary estrone and estradiol levels were strongly significantly associated with lower risk (top vs. bottom quartile RR estrone=0.52, 95% CI=(0.30–0.88); estradiol=0.51, 95% CI=(0.30–0.86)). Generally inverse, though non-significant, patterns also were observed with 2- and 4-hydroxylation pathway EM.
- Women with high urinary luteal estrone and either low or high plasma luteal estrone were at significantly lower risk compared with women with low plasma and low urinary estrone (urine/plasma high/low RR=0.56, 95% CI (0.32–0.97), high/high RR=0.65, 95% CI (0.43–0.99)). Similar associations were observed for urinary and plasma luteal estradiol. We also observed a similar pattern for both estrone and estradiol when we examined the combination of luteal urinary levels and follicular plasma levels (e.g., estradiol high/low RR=0.60, 95% CI (0.36–1.01), high/high RR=0.58, 95% CI (0.34–0.97)).

Ziegler, Regina et al. "Epidemiologic Studies of Estrogen Metabolism and Breast Cancer" in Steroids 2015 July: 99(Pt A): 67-75

- Since practically all EM in urine are conjugated, only total EM is measured in urine samples; in serum samples, both total and unconjugated EM are measured, and conjugated EM is calculated by subtraction
- An assay that reliably distinguishes serum estradiol concentrations in the low postmenopausal range (<110 pmol/L; <30 pg/mL), and at the even lower concentrations found in women being treated for breast cancer with aromatase inhibitors (~4 pmol/L; ~1 pg/mL), can be an important prognostic tool in the management of breast cancer, osteoporosis and bone fracture, cardiovascular disease, and possibly cognitive dysfunction (32,33). In addition, sensitive, accurate measurement of circulating estradiol is critical for epidemiologic studies of endogenous estrogen and disease risk and survival, as well as studies of the lifestyle, environmental, and genetic determinants of endogenous estrogen exposure
- In the postmenopausal breast cancer studies, the associations with ratios of estrogen metabolism pathways appeared independent of the recognized association of unconjugated estradiol with increased risk. If these biomarkers of estrogen metabolism are confirmed as reliable predictors of breast cancer risk, they might not only provide clues to mechanisms of breast carcinogenesis but also become useful clinically in prevention and treatment.

Pearls from Dr. Speroff

Breast and endometrium cells are similar

Page 624

Breast has alpha and beta receptors

Page 623

Progesterone inhibits estradiol induced proliferation in the breast

Page 652

Tamoxifen must be present in a concentration of 100-1000x greater than estradiol. Estradiol affinity is 100-1000x greater

Page 84

OTHER INTEGRATIVE STRATEGIES

Dietary Changes

- **Fiber consumption and breast cancer incidence: A systematic review and meta-analysis of prospective studies, April 6 2020**
  - *Eat more fiber.* Higher fiber consumption was linked to an 18 percent lower risk
- **Onion and garlic consumption may reduce breast cancer risk, September 23, 2019**
- **https://www.sciencedaily.com/releases/2019/09/190923155139.htm**
  - ***Spice with onion and garlic.*** **Daily consumption of onion and garlic linked to 67 percent lower risk.**
- **New study associates intake of dairy milk with greater risk of breast cancer https://www.sciencedaily.com/releases/2020/02/200225101323.htm**
  - Eliminate dairy
- **Substituting poultry for red meat may reduce breast cancer risk, August 7, 2019**
- **https://www.sciencedaily.com/releases/2019/08/190807092352.htm**

Dietary Changes- Coffee

- Coffee protects against breast cancer recurrence, detailed findings confirm, **April 21, 2015**
- **https://www.sciencedaily.com/releases/2015/04/150421084531.htm**
-
- Coffee reduces breast cancer risk, study suggests, **May 11 2011**
- **https://www.sciencedaily.com/releases/2011/05/110510211602.htm**

Environmental Detox

- **Exposure to BPA Substitute, BPS, Multiplies Breast Cancer Cells, April 3 2017**
- **https://www.sciencedaily.com/releases/2017/04/170403140605.htm**
- **BPA linked to breast cancer tumor growth, March 6 2014**
- **https://www.sciencedaily.com/releases/2014/03/140306163359.htm**
- **Skin**
- **Makeup**
- **Food**
- **Cleaning Products**

Toxic

PROTCOL FOR PREVENTION

1. Serum Lab evaluations
   - Possibly could do lab assessment every 10 years – starting at age 25 for those with FHMx
2. Increased surveillance- Start Mammogram earlier, consider MRI
3. Exercise
   - A meta-analysis revealed that women could significantly reduce the risk of breast cancer by approximately 25% if they exercise regularly
4. Diet changes
   - It has been suggested that dietary and environmental factors may be responsible for up to 50% of breast cancer incidence. A low-fat diet and a vegetarian diet decrease levels of sex-steroid hormones. These data suggest that reduction of serum sex-steroid hormone concentrations may diminish the risk of breast cancer
5. Check Estrogen Metabolism if Serum levels are high

Conclusion

- ✓ **Hormone levels DO** affect the risk of breast and endometrial cancer - both ENDOGENOUS and EXOGENOUS
- ✓ Make sure to **identify** patients who have a **risk** of impaired estrogen metabolism
- ✓ **Check** estrogen metabolism on ALL high-risk patients if you are prescribing HRT
- ✓ Take time to recommend **environmental detox** and **dietary changes**

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TaraScottMD